VOL. CLXXXII, No. 4 OCTOBER, 1931 No. 715

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

PROBLEMS OF PRESENT-DAY GASTROENTEROLOGY. By WALTER C. ALVAREZ, M.D. 441

CLINICAL OBSERVATIONS OF THE IMMUNIZING VALUE OF "NATURAL BACTERIAL ANTIGENS." STUDY NO. I.—PNEUMOCOCCI. By DON C. SUTTON, M.D., ARTHUR ISAAC KENDALL, PH.D., and ALBERT ROSENBLUM, M.D. 454

THE DIAGNOSTIC PROGRAM IN FOOD ALLERGY. By WARREN T. VAUGHAN, M.D. . 459

SYDENHAM'S CHOREA. By R. W. WAGGONER, M.D., Sc.D. 467

CREATINURIA IN HYPERTHYROIDISM. By EDWIN J. KEPLER, M.D., and WALTER M. BOOTHBY, M.D. 476

HEREDITARY AND FAMILIAL DIABETES MELLITUS. By IRVING SHERWOOD WRIGHT, A.B., M.D. 484

INTERPRETATION OF FLARIMETER TESTS. By L. MACKENZIE, M.D., P. V. WELLS, D.Sc., E. G. DEWIS, M.D., and L. S. YLVISAKER, M.D. 497

THE EFFECT OF BLOOD TRANSFUSIONS ON BONE-MARROW ACTIVITY AS INDICATED BY THE RETICULOCYTE. By CARL REICH, A.B., M.D. 513

PRIMARY HYPOCHROMIC ANEMIA (ERYTHRO-NORMOBLASTIC ANEMIA). A NEW TYPE OF IDIOPATHIC ANEMIA. By WILLIAM DAMESHEK, M.D. 520

IDIOPATHIC HYPOCHROMEMIA By EDWARD S. MILLS, M.D., M.Sc. 554

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 50

Contents continued on page x

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1931, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER
PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

THE ORIGINAL

IMPORTED FRENCH

Bacteriophage d'Herelle

FOR EXPERIMENTAL USE only, we now have available a limited supply of the original Bacteriophage-d'Herelle, imported from France. This will be distributed on request, in the interest of medical science and without cost, to physicians having important hospital connections.

There are four preparations of Bacteriophage-d'Herelle—all harmless even in very large quantities.

Bacté-Dysenteri-Phage (*Antidysenteric Bacteriophage*) is specific for bacillary dysentery and destroys the Shiga, Flexner and Hiss types of the dysentery bacillus.

Bacté-Pyo-Phage (*Antipyogenic Bacteriophage*) is specific for pyogenic infections and destroys staphylococcus, streptococcus, pneumococcus, B. pyocyaneus and other pus producing organisms.

Bacté-Intesti-Phage (*Intestinal Bacteriophage*) is a polyvalent preparation capable of destroying the bacteria of various intestinal infections. It is reported to be of value in infantile diarrhea, enteritis, colitis and other infectious diseases of the intestinal tract.

Bacté-Rhino-Phage (*Antirhinitis Bacteriophage*) is a polyvalent preparation reported to be of value for coryza, rhinitis, sinusitis and bronchitis.

Bacteriophage-d'Herelle is the *only* preparation available that is made in accordance with the rigid technique of Professor d'Herelle, the discoverer of Bacteriophage. Profits from its sale, when marketed, are to be devoted to scientific research.

Complete literature and a sufficient supply for clinical investigation will be sent on request to physicians having important hospital connections. This product is not yet available commercially in the United States.

Sole Agents for the U. S. A.

Anglo-French Drug Co.

(U. S. A.) Inc.

1270 Broadway New York, N. Y.

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1931

ORIGINAL ARTICLES.

PROBLEMS OF PRESENT-DAY GASTROENTEROLOGY.*

By Walter C. Alvarez, M.D.,

Associate in Division of Medicine, The Mayo Clinic; Associate Professor of Medicine, The Mayo Foundation, Rochester, Minn.

In my estimation the greatest problem that still faces the gastroenterologist is: Why does food go aborally down the bowel? Until the mechanism which normally keeps waves traveling down the stomach and bowel is known and thoroughly understood the physician must always feel somewhat embarrassed when he is asked to overcome dynamic or paralytic ileus, or when he is asked to stop nausea, regurgitation or vomiting; it must be obvious that one cannot hope to tinker successfully at a mechanism, the normal functioning of which he does not fully understand.

Problems of Physiology. *Gradients.* It now appears probable that peristaltic waves tend to travel aborally largely because the upper part of the bowel is more active, more irritable, and more responsive to every stimulus than is the lower part. Since the tonus and activity of the intestinal wall decrease gradually from duodenum to colon, it can be said that food follows a gradient of force similar to the one which causes oil to flow along a pipe line. This gradient of force in the bowel might conceivably be reversed if the muscle in the lower end of the bowel were to become irritated, as by inflammation, until it became as active and tonic as the muscle in the upper end usually is; and actually, Hosoi and I have produced such reversal in animals by injecting irritant substances into the tissues about the ileocecal sphincter. As we expected in these animals, the small

* Presented before the New York Academy of Medicine, April 17, 1931.

bowel often showed an inability to forward its contents; the local rhythmic movements were active enough, but the big traveling waves were hard to start, and when they did appear they traveled slowly and soon tended to fade out.

The gradient of force might also be reversed by the action of any poison that would injure the highly sensitive neuromuscular apparatus in the upper end of the bowel more than it would injure the less sensitive mechanism in the lower end. I think it probable that this is one of the ways in which some drugs produce nausea, and in which fatigue, exhaustion and infectious diseases upset digestion. As is well known, a man or woman who is coming down with a cold or who is suffering from tuberculosis loses appetite, and a dog with distemper refuses to eat. If the dog is fed forcibly the food will not leave the stomach, although there is no obstruction at the pylorus, and if one studies the intestinal gradient in such an animal it will often be found reversed. Hysterical women and frail weak girls often seem to have such a poor gradient of forces in the bowel that it is hard for them to get any food through in the normal direction but it is easy enough for them to pass it back the wrong way.

It is unfortunate that as yet we gastroenterologists are without any drug that can be counted on to steepen or to restore to normal these reversed gradients, and hence we have to get along as best we can with prescriptions for good hygiene, rest, tonic measures, and outdoor life. Surely, it will be a great day for us when someone discovers a drug that will always stop nausea and regurgitation and vomiting, and will make it possible for frail, neurotic, and exhausted women to eat with appetite and zest.

A few years ago Hosoi and I showed, as we had hoped to do, that the gradient of irritability down the bowel is commonly reversed in pregnant animals. This reversal seems to be due to an increase in the metabolic activity of the lower part of the bowel, an increase which is shared by most of the tissues in the neighborhood of the growing uterus. It now seems probable that a reversal of the gradient of forces in the bowel can be produced by any agency that will depress the functions of sensitiveness and activity more in the upper part of the bowel than in the lower part, or which will stimulate them in the lower part more than in the upper.

A theory becomes a valuable working hypothesis when it seems to explain and throw light on many facts of observation, and actually, the gradient idea offers we practising physicians and surgeons the only explanation we now have for many of those peculiarities of intestinal activity which we see in our daily work. It has also been helpful in suggesting useful therapeutic maneuvers. Thus, it can easily be seen that a digestive tract in which the forces are somewhat reversed is likely to work better if solid food is put into the stomach. The presence of such food will tend to increase the tonus of the muscle in the upper end of the tract and the gradient down the

bowel will thereby be steepened. On the other hand, the putting of irritant material into the rectum, especially after operations on the pelvic organs, should tend still further to reverse an upset gradient, and thus cause vomiting. Actually, surgeons have found after operations that the Murphy drip, if used to excess, will cause nausea and other discomforts.

It may be that one of the reasons why calomel works so well in some "bilious" persons is that it steepens the gradient of forces in the bowel and causes the current to set downward and not upward. This, of course, is pure conjecture, because, so far as I know, no one has studied the influence of calomel on the intestinal gradients.

The Nerves of the Tract. Although much of value has been learned about the various related gradients and the ways in which they can help to maintain the normal direction of peristalsis, much remains to be learned about the structure and functions of Auerbach's plexus, and about the ways in which it mediates conduction along the bowel. The work of several investigators has shown that often, as after operations, when the bowel appears to be paralyzed the muscle remains quiet, not because it has been weakened by toxins, but because it is inhibited by nervous action. Thus, the intestinal muscle of a dog that is dying of peritonitis will contract rhythmically and normally if the splanchnic nerves are out or if the bowel is excised and placed in warm oxygenated Locke's solution. One can see from this why it is that in some cases of dynamic ileus if nervous inhibition is removed by the induction of spinal anesthesia, the bowels will move immediately.

Some work which Hosoi and I did a few years ago on scores of rabbits convinced us that both the vagus and the splanchnic nerves serve largely as brakes to the bowel. Without these brakes the gut tends to respond to every stimulus, and the animals often die of diarrhea and inanition. This work, together with much else reported in the literature, left me strongly inclined to believe with Cannon that most of what has been written so convincingly about vagotonia and sympatheticotonia is wrong and without foundation in fact.

Indigestion is Produced by Motor Dysfunction. For the last 17 years I have felt so certain that gastroenterology is to advance only as more knowledge is secured in regard to the motor functions of the digestive tract, that I have been spending half of every day in a laboratory of physiology studying the movements of the stomach and bowel. To be sure, the secretory functions of the tract are also important and there is a great need for knowing more about them, but the symptoms of indigestion are, I believe, produced mainly by disturbances in the motor functions. As proof of this, I need only cite the fact that perhaps 1 of every 3 men and women, aged more than 60 years, is living fairly or quite comfortably with no free acid in the gastric juice. If, however, in one of these persons

there were to come a breakdown in the motor transport through pylorus or intestine, that man or woman would be forced, within a few hours or days, to consult a physician.

Gastric Secretion. It is sad to have to admit that after all the years spent in the study of gastric secretion our knowledge in regard to it remains elementary and insufficient. We physicians know a little about the concentration of hydrochloric acid in health and disease, but we cannot control it satisfactorily, and we still know almost nothing about the concentration of pepsin in various diseases. Worse yet, we do not know why the normal stomach does not digest itself and why the diseased one sometimes does. If Michaelis is right and the protection of living cells lies in the fact the lining membrane is made up of lipoids which are not digestible by pepsin, those investigators who are now searching for the cause of ulcer should be studying lipases and not hydrochloric acid.

Flatulence. There is much need for more knowledge in regard to the absorption of food residues and gases. It is known now that the gases which are being formed constantly in the bowel are normally being carried away by the blood stream and excreted through the lungs, but it is not yet known just how this mechanism is disturbed in persons who suffer with flatulence. It is even possible that in many cases it is not disturbed and that the offending gas is nitrogen, which represents the almost unabsorbable residue left from swallowed air. The next question is: Why do some persons swallow so much more air than others? The worst air swallower I ever watched back of the roentgenoscopic screen could get into his stomach perhaps 500 cc. of air while he was drinking a glass of milk, but neither he nor I could see wherein his method of swallowing was different from that of his more healthy fellows.

Functional Disturbances of Digestion. *Disturbances Due to Emotions.* The next big problem, which of course is but a continuation of the ones that I have just been outlining, is: What is the mechanism of the nervous or functional disturbances of digestion? Fortunately, there is now at hand some knowledge as to the ways in which emotion can affect the various functions of the digestive tract. Thus, it is known that mental distraction, fright, worry, disgust, or annoyance at mealtime can, for hours afterward, interfere with the emptying of the stomach. It is known also that these mental disturbances can either greatly delay or else markedly stimulate the movements of the bowel. Psychic upsets can also put a stop to digestion by drying up the various secretions that are normally poured into the various parts of the tract. The resulting failure of chemical digestion is followed by failure of absorption, and this produces irritation or inflammation of the mucous membrane of the bowel. This, again, produces more indigestion, and thus is started a vicious circle which can be broken only by careful dieting. Emotion can cause also blanching or blushing of the intes-

tinal mucosa much as it causes blanching and blushing of the skin, and such changes might account for disturbances in digestion and absorption. Everyone knows that anxiety and fright can cause diarrhea, and many physicians know that worry can cause constipation.

Indigestion Originating in Constipation. The presence of hard feces plugging the lower end of the colon will often lead to the accumulation of gas in the splenic flexure, and of feces in the cecum. The stagnation of foul material in the right side of the colon will in turn produce irritation and even actual typhlitis, and with this, there will be pain resembling that of appendicitis. In such cases, if the rectal plug can be removed gently, as by an enema of warm physiologic salt solution, all of the flatulence and pain and indigestion will be relieved.

Effects of a Coarse Diet. Many disturbances of digestion are doubtless due to the eating of rough irritant foods, poorly prepared foods, or foods to which the patient is sensitive. In such cases the prescription of a proper diet will bring relief, but in many others the most careful dieting will have little if any effect.

Constitutional Inadequacy. As already suggested in the first part of this article, many disturbances of digestion can best be explained on the assumption that the gradient of forces down the bowel has been flattened or reversed, perhaps by fatigue, exhaustion, nervous depression, or painful emotion. In many cases the primary defect seems to be a congenital or a hereditary one because several members of a family will complain all their lives of being easily fatigued, easily excited, and markedly disposed to suffer with headache, insomnia, and general nervousness. They appear to be constitutionally inadequate to stand the strain and stress of life. Thousands of these persons are now going from physician to physician in search of help; they constitute a large fraction of our clientele, and yet we often fail to recognize the underlying cause for their complaints. Instead of helping them to understand the true nature of their handicap, instead of teaching them that they must stop hunting for a complete cure, and instead of showing them how to live so as to get as much work as possible out of a defective piece of machinery, many of us put these patients through long and trying courses of examination and treatment; for weary months we "drain the gall bladder," we dilate hypothetic ureteral strictures, we treat hypothetic ulcers with Sippy cures, we remove teeth and tonsils, and sooner or later we explore the abdomen. Unfortunately, the more scientifically trained the physician, the more likely he is to offend against these poor patients because he knows of more things to do.

Migraine. Although migraine is, I think, a disease of the brain or of some phase of metabolism and not a disease of the digestive tract, it is of tremendous interest to the gastroenterologist because most of the patients with sick headaches go to him fully convinced that

if he would cure their digestive upsets they would be well. I am sorry to say that quite commonly physicians are so deceived by the presence of nausea, vomiting, and abdominal pain that the patient is put to the expense of one or more needless and useless operations.

Not infrequently, the symptoms suggest that cholecystitis may be present, but the wise clinician will continue to question the patient until he makes sure that there is never any indigestion between attacks and never an attack without the preliminary headache. He will know then, that the disease is not in the abdomen but probably in an irritable spot up in the brain from whence there spreads out down the vagus or splanchnic nerves a "storm" similar to that which produces the gastric crises of tabes or the vomiting of sea sickness. Even when gall stones are found their removal may have little if any effect on the course of the disease.

Recently a number of writers have come forward claiming that most cases of migraine are due to the eating of food to which the patient responds in an allergic way. I have seen a few cases in which headache did disappear after the elimination of certain foods, and I have found evidence of an allergic type of sensitiveness in many others, but my successes with dieting have been so few that I fear the cause of most cases of migraine has not yet been found. I think, however, that a promising lead has been opened and it should be followed out in every case with as much care as the intelligence and pertinacity of the individual patient will permit.

The difficulty is, that migraine is so often found in highly sensitive or distinctly neurotic persons who will not take good care of the brain; they work long hours, they pay little attention to the need for sleep, and in many ways they keep the cerebral cortex in such an irritable condition that many triggers here and there in the body will be able to start the attack.

There is evidence also that some of the attacks come at certain points in certain rhythmic cycles of metabolic activity which as yet are barely recognized and not at all understood. To me it has been suggestive that all of the research workers who have recorded daily the degree of activity of animals kept in cages have found remarkable cycles of increase and decrease. Some of these cycles are long and probably correspond to the menstrual cycle in women, while others have shorter periods. Already there is definite evidence that such cycles are present in men and women, and more must be learned about them.

It may be that knowledge in regard to these metabolic ups and downs and their mode of production will help later to explain the alternating cycles of well-being and of depression or feeling of toxicity which are seen in many psychopathic and otherwise constitutionally inadequate persons. Why is it that on some days they are full of energy and on others they wake up feeling weak and blue and unable to face the world and the work that they have to do?

Constipation. Reading the other day a translation of the Eber's Papyrus, a book which has come down to us from the time of the building of the Pyramids, I was struck by the fact that so large a number of these ancient prescriptions were designed for the relief of constipation. And here we are, 5000 years later, using some of the same drugs that are mentioned in that papyrus, and almost as ignorant as were the Egyptians in regard to the real causes of the disease. We physicians still must admit that in many cases there is no real or permanent cure for constipation. Even the bulky diets which are now so commonly used tend after a time to lose their efficacy just as laxatives do.

I have hopes that during the next decade some help will come from the neurosurgeon. He is now experimenting with sectioning of some of the nerves which produce spasm of the lower segment of the bowel, and something useful may come out of this work. It may be, also, that more of the patients with intractable constipation will be asked to submit to a transplantation of the terminal ileum to some point in the transverse colon. I see two main difficulties: one, that so many of the affected patients are too querulous and neurotic to be good subjects for any form of surgical intervention, and the other, that any operation for constipation which for a time seems to be very successful, later tends to lose its efficacy and the patient is back where he was before.

One helpful measure that I have discovered is the use of enemas of warm physiologic salt solution. In most cases of constipation the stagnation of feces is in the last few inches of the colon, and it would seem most logical to wash out this segment without upsetting and irritating the many feet of bowel up above. When one mentions an enema to many of these patients, they immediately say that the procedure has been tried and found unsatisfactory. These persons often have a very sensitive colon and if one tries to inject plain water or soapy water into it, there is much spasm and it may take hours of struggle to get the water in and then it may take hours to get it out. If, now, such a patient will put into the enema bag warm physiologic saline solution (a tablespoonful of table salt to 2 quarts of water) he or she will generally have no difficulty in getting it either in or out and there will be no irritation of the bowel and no passage of mucus afterward.

Physiologic salt solution will not irritate the mucous membrane of the colon and I cannot imagine how there could be any permanent injury. I believe, therefore, that physicians are not justified in warning patients as they now do against the frequent use of enemas. If many of the persons who now complain of flatulence and indigestion were only taught to remove, in this simple way, the fecal plug which obstructs the lower end of the bowel they would promptly get well.

Diarrhea. It is sad to have to admit that in many cases of diarrhea a definite diagnosis cannot be made. If examination of the stools does not show any sign of parasites, if the roentgenograms show a normally haustrated colon, and if the sigmoidoscopic examination shows a normal mucous membrane, the physician must feel more or less stumped. Diarrhea which comes only in the morning will sometimes be associated with achlorhydria, and in other cases it may be found that the attacks are due to excitement or worry.

Some types of diarrhea seem to be due to a familial predisposition; the stools may be loose for many years and yet the patient is not ill. In many other cases a cause cannot be found and, actually, I have seen a few persons who died of diarrhea and yet the pathologist was unable to say what had gone wrong with the digestive tract. Obviously, there is need for further research in this field. In this connection it may be interesting to note that in a large percentage of the experiments in which my assistants and I cut the splanchnic or vagus nerves in rabbits the animals died later of diarrhea and inanition; it seemed as if the brakes had been taken off the bowel.

It is conceivable, also, that in some cases of diarrhea something has gone wrong with the function of absorption. I can remember studying a young woman with a diarrhea which had been present off and on for years without inconveniencing her to any great extent. Roentgenologic examinations showed that the feces in the transverse, ascending and descending portions of the colon were normally desiccated and formed, and yet those that came from the rectum were soft and even watery. It seemed obvious, therefore, that something had gone wrong with the absorbing mechanism of the colon and that water was actually coming back from the blood into the sigmoidal and rectal segments. I mention this observation simply to show one way in which the problem of diarrhea will have to be studied.

"Functional" Troubles that May Have an Organic Basis. I have now offered explanations for the symptoms of a large number of patients in whom macroscopic lesions are rarely found at operation or necropsy. Unfortunately, there still remains a large number of persons who, while they do not seem to be suffering with any one of the few definite diseases which are known to occur in the abdomen, are yet too sensible and too severely incapacitated to be dismissed as "neuros." Many of these persons are seriously ill; their troubles perhaps came suddenly out of a clear sky; they are perhaps waking at night with distress, and perhaps they have already submitted to one or more exploratory operations. If they have not, the wise physician will not care to order one because he knows that, with the peculiar history and the sheaf of negative laboratory reports, it will probably be useless to open the abdomen.

What is wrong with these persons? My own impression is that many of them must have some lesion in the digestive tract or in its nerves and related ganglia, but what it is or where it is, I have but a faint idea.

Gastritis and Enteritis. In many of these cases some physicians tend to fall back on the diagnosis of "gastritis," but the available evidence indicates that this is not a common disease, and even if it were present, it is doubtful if it would always produce symptoms. I think it more probable that at times some form of enteritis is present, and experiments on animals have shown that inflammation in any part of the wall of the bowel will produce disturbances of digestion and will give rise to symptoms.

I feel sure that at times there is some form of inflammation in the region of the ileocecal sphincter which can produce a syndrome similar to that of chronic or recurrent appendicitis. To be sure, many of the patients who do not get well or who fail to stay well after appendectomy are neurotic or are suffering with duodenal ulcer, cholecystitis, mucous colitis, or constipation, but there are some who continue to suffer with symptoms that are typical of a smouldering appendicitis, and in them I feel sure that there must be some source of irritation in the ileocecal region.

Years ago I prophesied that some form of duodenitis would some day be found to account for symptoms and Roentgen ray findings closely resembling those of ulcer, and today it is a well-recognized disease. Similarly, I think it safe now to prophesy that several new diseases will be found along the course of the bowel when the pathologist takes time to look more closely for them.

Hepatitis. The presence of some degree of hepatitis is commonly noted during operations on the gall bladder, and I think it probable that it produces symptoms, and that in some cases it accounts for the postoperative persistence of a clinical picture that resembles that of cholecystitis. It has always seemed to me that when the surgeon removes a diseased gall bladder he must often leave behind in the liver much of the disease he was trying to cure. For this reason the wonder to me is not that he sometimes fails to relieve the symptoms but that he so often succeeds in doing so. Apparently, when the main focus of infection is removed, the other parts of the biliary system are better able to clear themselves of infection.

Cirrhosis of the Liver. It would seem that cirrhosis of the liver should, even in the earlier stages, produce some symptoms, and perhaps at times it does account for cases of severe, otherwise unexplainable, flatulence with soreness in the right upper quadrant. The objection to this theory is that occasionally one sees patients who have recovered from symptoms of cirrhosis and who continue to show a considerable degree of dye-retention with the Rowntree-Rosenthal test, but who do not suffer with any symptoms of indigestion. In other cases, when the physician is disappointed over his

failure to show the expected defect in liver function, he must admit that this probably does not mean much because the liver has many functions, most of them as yet unassayable, and all of them with such a large factor of safety that by the time a defect can be shown, the patient is about ready to die.

In spite of all these difficulties, I still feel that a clinical picture which resembles that of cholecystitis is probably often produced by a smouldering infection in the liver. Sometimes this infection will invade joints, sinuses, prostate, or heart. I believe, therefore, that one of the drugs that is most needed in gastroenterology today is one which will help the body in overcoming this smouldering type of septicemia.

Pancreatitis. One wonders, at times, if perhaps a mild pancreatitis might be present and responsible for vague distressing symptoms in the abdomen, and for pains shooting straight back into the spine or downward toward the hypogastrium. Against this theory is the fact that oftentimes at necropsy fairly severe pancreatic infection, destruction, or irritation, such as is produced by a perforating ulcer or by gall stones, will be found when the history had not led the physician to suspect its presence. In other words, the pancreas seems to be so poorly supplied with sensory nerves that it does not always complain when it is hurt.

Both with cirrhosis and pancreatitis the presence or absence of symptoms must, of course, depend partly on the degree of sensitiveness of the individual. As Libman has pointed out, the insensitive type of person will remain at work quite unconscious of illness long after some severe disease has begun to gnaw at his vitals.

Mild Infection with Neurotropic Viruses. A type of infection that I think can be held responsible for many poorly explainable "nervous breakdowns" is one with an encephalitic virus of low virulence. This is but a theory of mine but it is based on a number of observations. It is well known that in some laboratories almost every other supposedly normal rabbit is a carrier of the encephalitic virus, and I strongly suspect that some men and women are similarly affected. When the body resistance is lowered by some infection such as that of vaccinia or influenza, encephalitis will sometimes flare up in such a way that the conclusion must be that the virus was already present in the brain. Similarly, a cold will often bring on an attack of labial herpes, which is due to a neurotropic virus almost indistinguishable from that which produces encephalitis.

It may be that the filter-passing organism which produces colds has at times a neurotoxic effect, or it may be that its coming stirs into activity a neurotropic virus that is always present. Certain it is that in some persons a very slight cold or sinusitis will have a markedly incapacitating effect on the brain. I have been struck also by the fact that occasionally, following an injury to the head or a flare-up of infection in the inner ear, the patient will die of acute meningitis, and at necropsy it will be evident that the acute

disease was superimposed on a chronic meningitis and encephalitis which had not been recognized during life. I have also seen a few nervous, incapacitated persons who, after having for some time been reviled and sneered at as "neuros," developed masklike faces and eventually died with definite encephalitis. It may well be, therefore, that at some time in the future, the gastroenterologist and the neurologist will be more keenly on the watch for mild infections with neurotropic viruses.

Mesenteric Lymphadenitis. There is one place in the abdomen in which infection can often slumber and this is in the lymph nodes of the mesentery. It has been shown by a number of investigators that bacteria are constantly getting through the intestinal wall only to be stopped in the second line of defense in these nodes, and I have seen a number of cases in which I felt fairly sure that the symptoms of indigestion, abdominal pain, weakness, and slight fever were due to some chronic infection which had overwhelmed these nodes and had caused one or two of them to become calcified and visible in the roentgenograms.

Disturbances in Circulation. Considering the tremendous importance of the portal circulation, it is unfortunate that so little is known about it either in health or disease. Marked degenerative changes in the mesenteric vessels are often found at necropsy, but as yet I know of no one who has attempted to correlate these changes with the symptoms presented by the patient before death. It might well be that many of the effects of emotion on the digestive tract are produced through changes in the caliber of the gastrointestinal vessels. It is well known that peptic ulcers are highly sensitive to nervous influences and it may be that vasomotor spasm, nervously produced, is, at times, lasting enough to produce first, anemia of the tissues, and then autodigestion. It is known also that some of the peptic ulcers and especially those that appear suddenly in older persons are due to the plugging of small gastric or duodenal arteries; the resulting shut-off in circulation produces an anemic infarct and then an ulcer.

Diseases of Nerves. Another possible cause for disturbances of function in the digestive tract is disease of the abdominal nerves and their ganglia. Many writers have described histologic changes in these nerves but much work remains to be done by more careful and more experienced investigators who will first make certain what a normal ganglion should look like.

I have of late seen several patients with constant upper abdominal pain somewhat resembling that of gall bladder disease but too constant and too little influenced, if at all, by the taking of food. In these cases the cause seemed to be an infection of nerve roots with the virus of herpes zoster. In one case the pain continued for months after the healing of the blisters and in another it was present for weeks before they appeared. The physician will suspect that such injury to the nerves is present when he finds that the pain is

constant hour after hour and day after day and that it is without relation to meals. In some cases pain in the upper abdomen is due to arthritis of the lower dorsal spine with involvement of nerves and muscles.

Pyorrhea. I have seen a few cases in which I suspected that the cause of epigastric pain and distress was swallowed pus coming from pyorrhea pockets, and in several of these persons the removal of a few teeth worked a cure within a remarkedly short time.

Pseudo-ulcer. A group of patients who greatly interest me complain of symptoms which are similar to those of ulcer, but usually not quite the same. Commonly the distress is too persistent; that is, it does not come in attacks with intervals of complete relief. Sometimes also the pain will be present in the morning before breakfast or it will not be relieved in a typical way by the taking of food or alkalies. The expert can often tell from the history that the trouble is probably not due to an ulcer and he will be prepared for the negative report of the roentgenologist. That this report is generally correct is indicated by the fact that some of these patients have been operated on and an ulcer has not been found. Many of them have a decidedly hyperacid gastric juice but this cannot be relied on to account for the symptoms because it is found so commonly in persons who have no discomfort or indigestion.

In many cases the disease seems to be related to nervousness, overwork, and unwise living, and it is best treated by ordering a vacation, by interdicting the excessive use of tobacco, and by changing, if possible, the patient's habits of living and eating. Often nerve sedatives will work better than alkalies.

The question, of course, that bothers these patients is: Is an ulcer going to develop some day? My impression is that perhaps in most cases it will not, but as yet I have no statistical data. All I can say is that I know a number of men who have had the symptoms and the hyperacidity for 10 years or more and who as yet show no sign of ulcer.

Definite Organic Disease. *Peptic Ulcer.* Every gastroenterologist, of course, must be keenly interested in the problem of peptic ulcer. What is the cause and why are some persons so highly predisposed to the disease that if one lesion is cut out another will take its place? Mann and his coworkers, who have produced ulcers at will by shunting the alkaline juices of the duodenum into the ileum, have shown that the acidity of the stomach has something to do with the problem, but there are many observations which indicate that there are other more important factors. There are countless persons with marked hyperacidity who do not develop ulcers and there are others with low acids who have one ulcer after another. I suspect, therefore, that we physicians have for a long time been barking up the wrong tree. Some parts of the answer to the problem will doubtless be found through further study of gastric acidity, but it is time now that investigators turned to the study of

some of the other possible factors. It seems to me that we should be learning more about the behavior of pepsin, gastric lipase, mucus, and the dilating fluid in health and disease.

In view of the intimate connection between the symptoms of ulcer and the psychic reactions of the patient it is important to learn more about the ways in which emotion can affect the various secretions of the stomach, duodenum, pancreas and liver. The work of Mann, taken together with the many stories that patients tell about the intimate relation between nervous strain and flare-ups of ulcer symptoms, makes me wonder if duodenal ulcers might not be produced sometimes by a temporary psychic shut-off in the alkaline secretion of the pancreas. It is conceivable also that a nervous spasm of the gastric and duodenal bloodvessels comparable to that which is seen in the hands and feet in Raynaud's disease might keep the gastric or duodenal mucosa anemic long enough so that autodigestion could take place and ulcers could form.

Unfortunately, any really adequate and satisfactory theory of ulcer causation must account for a host of facts and must explain not only the formation of duodenal ulcer but also of gastric and gastrojejunal ulcers. Perhaps, there are different types of ulcers at different ages and in different situations, and we may have to study the causes of all these types. Any adequate explanation of ulcer formation must throw light also on the mode of production of hunger pain. Although much valuable work has been done on the subject, no one of the theories in regard to the causation of ulcer pain satisfies me. It has not yet been explained why the attacks of pain come and go so suddenly, and why alkalies will often give relief when operation or necropsy shows that there has been no break in the continuity of the mucous membrane and no ulcer into which the acid gastric juice could eat.

Abdominal Pain and Its Relief. Gastroenterologists still need to know a great deal more about the points of origin and modes of conduction of abdominal pain. It is curious that in a patient under local anesthesia the surgeon can cut the stomach and bowel and can burn holes in it with the cautery without causing distress, but let him just pull on the mesentery or place a clamp on a bloodvessel or even wash off the peritoneal surface of the stomach with warm physiologic salt solution and the patient may nearly jump off the table. Even the injection of a little air into the peritoneal cavity will produce almost unbearable pain in the upper part of the abdomen.

Students of the subject now agree that most, if not all, of the nerve fibers that carry pain sense leave the abdomen by way of the splanchnic nerves. These nerves can be blocked by the injection of drugs from the back, and I believe that the time is coming when more frequently we physicians will be calling in experts in local anesthesia and neurosurgery to help us in giving relief to some of the patients who complain bitterly of pain about the stomach, gall bladder, or colon. We can perhaps learn to make life bearable for

persons who have not received relief from cholecystectomy or gastroenterostomy or appendectomy. It may be that in a given case the anesthetist will first see if the pain can be blocked by injection of one or more nerve roots or rami communicantes. Once the exact point at which blockage can be obtained is known, alcohol may be injected or the nerve may be cut. In a few of the most severe cases the spinal cord may be exposed and small nicks may be made on either side to destroy the tracts which carry sensations of pain. Much work along this line is being done and I hope that something helpful will come out of it.

Summary. This paper cannot easily be summarized: about all one can do is to add an index. The subjects treated are: the mechanism of aboral peristalsis; gradients; the nerves of the digestive tract; the mode of production of symptoms of indigestion; gastric secretion; flatulence; disturbances of digestion due to emotion, to constipation, to coarse diet, to constitutional inadequacy, and to migraine; the causes of constipation and diarrhea.

Particular attention has been given to those so-called functional troubles that may really have an organic basis. They might be due to gastritis, enteritis, hepatitis, cirrhosis of the liver, pancreatitis, mild infection with neurotropic viruses, mesenteric lymphadenitis, disturbances in the circulation of the stomach and bowel, or diseases of the nerves in the abdomen.

Suggestions are given as to the possible cause of peptic ulcer and pseudo-ulcer and as to the ways in which abdominal pain may some day be relieved.

CLINICAL OBSERVATIONS OF THE IMMUNIZING VALUE OF "NATURAL BACTERIAL ANTIGENS."

STUDY NO. I.—PNEUMOCOCCI.

BY DON C. SUTTON, M.D.,

ASSOCIATE PROFESSOR IN MEDICINE, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL; ATTENDING PHYSICIAN, COOK COUNTY HOSPITAL,

ARTHUR ISAAC KENDALL, PH.D.,

PROFESSOR OF BACTERIOLOGY AND HEAD OF THE DEPARTMENT OF RESEARCH IN BACTERIOLOGY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL,

AND

ALBERT ROSENBLUM, M.D.,

FORMERLY RESIDENT PHYSICIAN, MEDICAL SERVICE, COOK COUNTY HOSPITAL, CHICAGO, ILL.

(From the Department of Research Bacteriology, Northwestern University Medical School, and the Medical Service, Cook County Hospital.)

THE specific therapy of pneumonia, as in other acute infections, has taken two courses, namely: (1) The production of passive immunity by the introduction of immune serum; (2) the production of active immunity by the introduction of specific antigens.

1. *Passive Immunity.* Because of the established value of specific antisera in such diseases as diphtheria and tetanus, the greater amount of work has been done in the production and study of such an immune serum for pneumonia. This line of research was greatly accelerated by the report of Cole[1] and his coworkers (1915) of an improved serum for Type I pneumococcus. More recently a serum prepared by the methods of Felton has been intensively studied by Park,[2] Cecil,[3] Bullowa,[4] Rosenblüth.[5] This serum, while polyvalent for Types I, II and III pneumococci, is most effective in Type I infection.

Cecil[3] believes that the maximum reduction of deaths in Types I and II infection has been reached "because this serum is practically 100 per cent effective in the treatment of experimental pneumonia in monkeys. However, in humans we have added the fact that mostly middle-aged and elderly people are attacked, that many of these are alcoholic or have some other systemic disease." 2. *Active immunity* has been produced in animals by Cecil[6] and Zinsser.[7] The production of specific antiserum is the result of active immunity produced in the horse.

Lister,[8] working among the miners of the Transvaal, found that the incidence of pneumonia could be greatly lowered by the use of an immunizing vaccine, not a single case of pneumonia occurring in a period of 9 months in 10,000 recruits. Cecil[9] and his coworkers found that the immunization of troops at Camp Upton, in 1918, reduced the incidence of pneumonia from 30 to 2 per 1000. Lister[8] and Lambert[10] reported a marked reduction in the death rate in cases of pneumonia treated with pneumococcus vaccine.

One of us (Sutton[11]) studied a commercial mixed vaccine similar to that studied by Lambert. Later this vaccine was simplified so that it contained only pneumococci and streptococci. These vaccines were prepared by sterilization with concentrated tricresol, which in the final suspension was diluted to from 2 to 4 per cent.

When this vaccine was discontinued, in 1928, another commercial vaccine was selected because it is sterilized with heat. The results with this latter vaccine were extremely disappointing, the death rate in the treated cases being much higher than in the controls.

During the period before 1930 various methods of preparation of bacterial antigens were studied. These studies brought out the importance of using only the bacterial cell washed free of its medium and excreta; further, that the ideal antigen is as near as possible to the living cell.

Quastel[12] introduced the term "resting" bacteria to designate organisms that are fully mature and endowed with their full potentiality for metabolism, but constrained from multiplication by the withholding of substrates essential for their continued growth. Kendall,[13] studying "resting" bacteria, states: "Bacteria in the 'resting' state are harvested at the height of their growth and

activity, from suitable culture media, washed free from all traces of cultural medium by repeated suspension in physiologic solution of sodium chlorid and centrifugation, and, finally, vigorously aërated to eliminate autoöxydizable substances." "Resting" bacteria initiate chemical changes in substrates which they, as proliferating bacteria, subsequently use for their energy requirements. Prepared in the manner described, they do not multiply unless a suitable source of nitrogen is available.

Resting bacteria are possessed of all the antigenic properties of actively proliferating bacteria, but if used as antigens animal tissues would furnish the nitrogen necessary for multiplication. The addition of a substance that will prevent growth of the bacteria in the presence of nitrogen is then necessary before they may be used as clinical antigens. The substance used should, ideally, prevent proliferation without change in the constitution of the bacterial cell.

Such a preparation of bacteria is the nearest safe approach to a perfect bacterial antigen. This we have called "natural bacterial antigen." Studies of such "natural bacterial antigens" clinically and with laboratory animals have shown that such antigens are remarkably free from reaction, either local or general. For the sake of brevity the term "antigen" will be used hereafter synonymously with natural bacterial antigen. The methods of production of "natural bacterial antigen" will be discussed in a later paper.

Similar preparations of Streptococcus hemolyticus, nonhemolyticus, viridans and staphylococci have been prepared for use as antigens in other infections, and have been found to be free from reaction, either local or general. Powell and Jamieson[14] "found that antigens prepared in a manner used in the preparation of 'natural bacterial antigen' contain intact the more labile antigenic fractions, such as the flagellar antigen. Such antigens produce more potent antibodies in treated animals than those prepared by heat or phenoloid preservatives. This was shown readily with saline suspensions of such bacteria as typhoid, pertussis and meningococcus."

From these experiments they conclude: "Such antigens constitute the closest artificial approach to living bacterial antigens as found in the tissues of the host in natural diseases. This is concluded from experience in using such antigens in the immunization of animals for the production of antiserum."

The question with regard to the treatment of pneumonia by active immunization is not whether an active immunity can be produced, but whether immunity can be produced rapidly enough during the course of the disease to be effective before death occurs. Zinsser found that by the fifth day sufficient antibodies may be produced in rabbits to protect them from lethal doses of pneumococci. From this work he concludes that, inasmuch as in human beings death usually occurs after 6 or 7 days, vaccine, even in severe

pneumonia, might produce immunity early enough to throw the balance in favor of the patient.

Kline and Winternitz,[17] by injections, showed that a large part of the capillary bed is closed by fibrin in pneumonic lungs, and conclude that this may be responsible for the restricted action of serum in this disease.

Our experiments have been carried out in Ward 64 (an adult male ward) of Cook County Hospital. All medical cases, irrespective of diagnosis, are assigned to a medical service, in rotation, by the general admitting service. There are two medical services in Ward 64—Drs. Sutton and Keeton, and Drs. Loeb and Trace. All cases are in the same unit and receive the same treatment, with the exception that those on the Sutton-Keeton service receive in addition the "antigen." This is immediately administered in doses of 1 to 1.5 cc. every 6 hours until the temperature is normal, and then every 12 hours, for 48 hours. Injection is made at four different points, usually in the arm and legs, with the idea that small doses are more rapidly assimilated and that a greater number of lymph glands receive the antigen. The injections are made barely under the skin.

The final development of the "antigen," the results of the use of which we report in this paper, was due to the results previously obtained with commercial vaccines, which are tabulated in Table 1 in conjunction with a summary of the results of Lambert. In these figures and all others given in this paper those cases dying within 24 hours of admission to the hospital have been eliminated; otherwise no selection has been made except as stated below:

TABLE 1.—TOTAL COMMERCIAL VACCINES, WARD 64, COOK COUNTY HOSPITAL, CHICAGO, 1926–1927, 1927–1928: COMBINED WITH LAMBERT'S RESULTS AT BELLEVUE HOSPITAL, NEW YORK.

	Treated with vaccines.			Controls.		
	Total cases.	Died.	Mortality, per cent.	Total cases.	Died.	Mortality, per cent.
Cook County cases	262	80	30.4	299	128	42.8
Lambert's cases	221	47	21.2	286	116	40.5
Total cases	483	127	26.3	585	244	41.7

In the total series 483 patients (Table 1) were treated with commercial vaccine, with 127 deaths, a mortality of 26.3 per cent. As controls, 625 cases were used, with 259 deaths, or 41.7 per cent—a reduction of deaths following the use of vaccines of 15.4 per cent, or a reduction of 37.1 per cent in mortality.

The work with the "natural bacterial antigen" began in January, 1930. During 1930 the pneumonia incidence was low, and as the study was under the control of a resident (Dr. Rosenblum), some cases in other wards were treated. During January of this year (1931) the cases are from Ward 64 only. As the number of control

cases for this period is relatively small (41), the average of all controls is also used in Table 2. As a further control, all the adult cases of lobar pneumonia (no children are included in any of this study) occurring in the hospital during the years 1927, 1928 and 1930, exclusive of 24-hour deaths and those previously used as treated cases or controls, were tabulated. The year 1929 is not included because no cases were treated with "antigen" during that year, this being the period during which various methods of preparation were studied. During this period of 1927, 1928 and 1930 there were 2679 cases of lobar pneumonia, with 894 deaths, or 33.3 per cent.

TABLE 2.—RESULTS OF TREATMENT OF PNEUMONIA WITH "NATURAL BACTERIAL ANTIGEN" COMPARED WITH CONSECUTIVE CONTROLS, AVERAGE OF CONTROLS OVER FOUR YEARS, AND WITH 2679 CONSECUTIVE CASES OF LOBAR PNEUMONIA, EXCLUSIVE OF CASES PREVIOUSLY COUNTED AS TREATED OR CONTROLS.
(Those cases dying within 24 hours of entrance to hospital have been omitted.)

Treated with bacterial antigen.				Control cases.		
Total cases.	Died.	Mortality, per cent.		Total cases, Ward 64.	Died.	Mortality, per cent.
129	29	22.5		339	143	42.1
			Cases of lobar pneumonia	2679	894	33.3
			Ward 64, 1930 . . .	41	17	42.5

It will be noted that the term "lobar pneumonia" has been used only in this last group of cases which are used as controls. However, in the other group all cases, both treated and controls, included lobar pneumonia, bronchopneumonia and various so-called terminal pneumonias. Thus it will be seen that the "antigen" treated cases gave favorable results, even when compared with a large number of lobar pneumonias.

Of the 129 cases treated with the "antigen" 29 died, a mortality of 22.5 per cent. Compared with all controls (339 control cases in Ward 64, 1926 to date—except 1929—with 42.1 per cent mortality) this shows a decrease of 19.6 per cent, or a percentage reduction of 46.5 per cent. If these antigen-treated cases are compared with a large series of straight lobar pneumonia (33.3 per cent mortality) there is a decrease of 10.8 per cent, or a reduction of 32.7 per cent.

It is believed that these results offer strong evidence that bacterial antigens are of value in the treatment of all types of pneumonia. Further, in view of the poor results obtained by Sutton with a heat-killed vaccine, the better results obtained with a commercial vaccine, and the still better results with a method of preparation which changes the bacterial protein the least, we are led to believe that the variable results from different antigens depend largely upon the method of preparation. If this be true it then becomes necessary to restudy the entire field of vaccine therapy.

Conclusions. 1. An improved method is suggested for the preparation of bacterial antigens.

2. Bacterial antigens prepared in this manner are nontoxic.

3. Bacterial antigens may be given early in the disease, without awaiting the typing of the pneumococcus.

4. The results with "natural bacterial antigen" are not spectacular, but they compare favorably with the results reported with the use of antipneumococcic serum.

5. As the results with "natural bacterial antigen" are on even terms with the specific sera, it should be used until its value is determined.

NOTE.—The antigen used during 1930 was made according to our methods under the personal supervision of Mr. Jamieson and Mr. Powell of the Biologic Research Division of Eli Lilly & Sons Company.

BIBLIOGRAPHY.

1. Cole, R. I.: Monograph No. 7, Rockefeller Inst., 1915.

2. Park, W. H., and Cooper, Georgia: Antipneumococcus Serum in Lobar Pneumonia, J. Am. Med. Assn., 1928, **90**, 1349.

3. Cecil, R. L.: Specific Treatment of Lobar Pneumonia, Arch. Int. Med., 1928, **40**, 295.

4. Bullowa, J. G. M.: Use of Antipneumococcic Refined Serum in Lobar Pneumonia, J. Am. Med. Assn., 1928, **90**, 1354.

5. Rosenblüth, M. B.: Ibid., p. 1351.

6. Cecil, R. L., and Blake, F. G.: Studies on Experimental Pneumonia. IV. Results of Prophylactic Vaccination Against Pneumococcus Pneumonia in Monkeys, J. Exp. Med., 1920, **31**, 519.

7. Zinsser, H.: Immunological Consideration of Pneumonia and Discussion of Rational Basis for Vaccine Therapy, New England Med. J., 1929, **200**, 853.

8. Lister, Sir Spencer: The Use of Pneumococcal Vaccine, J. Indus. Hyg., 1924, **6**, No. 2, 45.

9. Cecil, R. L., and Vaughn, H. F.: Results of Prophylactic Vaccination Against Pneumonia at Camp Wheeler, J. Exp. Med., 1919, **29**, 457.

10. Lambert, Alexander: The Use of Mixed Stock Vaccines in Pneumonia, Trans. Assn. Am. Phys., 1926, **41**, 224.

11. Sutton, Don C.: Vaccine Therapy in Pneumonia (A Preliminary Report), Illinois Med. J., 1928, **53**, 280.

12. Quastel, J. H.: Quoted by Kendall.

13. Kendall, A. I., Friedemann, T. E., and Ishekawa, M.: J. Infec. Dis., 1930, **47**, 186.

14. Powell, H. M., and Jamieson, W. A.: Merthiolate as a Germicide, Am. J. Hyg., 1931, **13**, 296.

15. Powell, H. M., and Jamieson, W. A.: Merthiolate as a Preservative for Biological Products, Am. J. Hyg. (in press).

THE DIAGNOSTIC PROGRAM IN FOOD ALLERGY.*

BY WARREN T. VAUGHAN, M.D.,

RICHMOND, VA.

FOR the purposes of this discussion we shall adopt a broad interpretation of the term food allergy as brought out in the following illustration. If, following a banquet, most of the participants

* Read as a part of a symposium on the Relation of Gastroenterology to Other Fields of Medicine, before the Thirty-fourth Annual Meeting of the American Gastroenterological Association, Atlantic City, May 4, 1931.

become ill, something was wrong with the food. If, on the other hand, with all eating the same food only one individual becomes ill, something was probably wrong with that individual. The first was an instance of food poisoning, the second of food allergy.

Symptoms Referable to the Enteric Tract. *Grande Anaphylaxie.* The "grande anaphylaxie" of the French, or acute anaphylactic shock, is the most startling and tempestuous of the responses to allergenic ingestants. Fortunately it is exceedingly rare. It consists in a severe acute reaction with nausea, vomiting, diarrhea, sometimes bloody, violent pain, often urticaria, circulatory collapse and even death within minutes or hours after eating the allergenic food.

Acute Food Allergy. Probably the two most nearly pure allergic responses are the gastric response, with nausea and vomiting and sometimes diarrhea promptly after eating the allergenic food, and the colonic response, with allergic colitis usually of the mucous colitis type. Often allergic digestive disturbances are accompanied by attacks of urticaria or angioneurotic edema, and one frequently obtains the history of other allergic manifestations either in the patient himself or in his family. But neither of these need necessarily be present.

Subacute and Chronic Gastrointestinal Allergy. Subacute or chronic abdominal allergy may manifest itself as a hyperperistalsis, especially in the colon, and with an increased secretion of mucus, in which eosinophils and Charcot-Leyden crystals may be found. Diarrhea is not a necessary accompaniment. Just as nervous indigestion may produce either diarrhea or constipation, food allergy may manifest itself with either of these responses. In either case we are dealing with smooth muscle spasm.

Cyclic vomiting is, in my experience, not infrequently a manifestation of food allergy. I have under observation just now 3 children with cyclic vomiting, 1 of whom has an associated allergic headache, while the other 2 have associated asthma. Balyeat[1] has recently presented evidence that the child with cyclic vomiting is likely to become the adult with migraine.

When we consider the type of pathologic response with muscle spasm, serous exudation, edema or internal hives, hyperemia and increased catarrhal secretion of the lining mucosa; and when we realize that the shock tissue may lie anywhere from the mouth to the anus and that in one individual different levels may be responsive at different times, we can more readily understand the frequent indefiniteness and variation in symptomatology in the individual case.

Allergy Complicating Organic Gastrointestinal Disease. While in my experience colonic symptoms most frequently accompany abdominal allergy the symptoms may closely imitate those of ulcer, appendicitis or of bile-tract disease. Indeed, food allergy may actually accompany a true organic state, thereby complicating the picture and the treatment.

A person with true cholecystitis will often remark that he cannot eat certain specific foods without exacerbation of symptoms. Here I believe we are often dealing with an associated food allergy in which ingestion of the specific allergen produces a local allergic response in the bile tract with resultant exacerbation of the cholecystitis. Valy Menkin[2] has demonstrated that foreign protein introduced into the circulating blood accumulates in an inflamed area, where it is found in greater concentration than in the normal tissues. He thus confirms the earlier work along the same line reported by Auer.[3]

Methods of Study and Treatment. I would divide the history of dietary treatment based on allergy into three epochs. The first, before the days of clinical allergy and skin testing, is represented by the empirical diet lists with which we have all been familiar in the past. To a certain extent they were based on experiences with cases of food idiosyncrasy, and included for a given symptom complex those foods which had been found by experience to be least productive of symptoms in the largest majority of individuals. Such were the diets for gall-bladder disease, mucous colitis, and the more obscure forms of chronic indigestion.

The second epoch was ushered in with the development of the sensitization test, when it seemed probable that by the simple process of applying solutions of the food allergens to the abraded skin, one could determine definitely to what food a patient might be intolerant. This was a decided improvement, and those who have used the method have clearly established that many allergenic foods can thus be discovered. At the beginning it appeared to be a splendid stereotyped method for determining the appropriate diet in the individual case. But as time went on even the enthusiast in skin testing was forced to the conclusion that some foods which definitely disagreed would not infrequently fail to give positive cutaneous reactions and that some that gave positive reactions would not be productive of symptoms.

So, in the third epoch in which we now find ourselves, we observe a combination of the methods of the first two with, in addition, a more rational and scientific systematization.

The allergic concept has taken food idiosyncrasy out of the limbo of curiosities and has placed it in the group of diseases of known etiology. The sensitization reaction has explained food idiosyncrasy and has enabled us to recognize hitherto unrecognized offending foods. This is especially true of the foods which are eaten daily and which therefore remain otherwise unsuspected. Realization of the deficiencies of the skin-test method have led to the third epoch, represented by the diagnostic use of the food diary and the trial diet.

The History. The anamnesis is as important in the case of allergy as in a neuropsychiatric case. From the past history and

the family history one will determine the probability of an allergic state, bearing in mind, of course, that such may exist in spite of an otherwise entirely negative personal and family history. The patient will sometimes suspect certain foods, and at times a careful discussion of each attack will suggest previously unsuspected foods. A history of seasonal variation will occasionally furnish good clues.

Physical and Laboratory Examination. It is only necessary to state here that the allergist who fails to make a thorough study of his cases from all angles, including roentgen-ray examination when necessary, will often fail to recognize other associated organic diseases in the gastrointestinal tract and elsewhere and will, as a consequence, fail in his treatment, in a measure proportionate to the importance of the associated disease.

Skin Testing. Regarding methods of skin testing I shall only say that both the scratch method and the endermic or intradermal technic have a distinct place. The latter is much the more sensitive but for safety's sake should not be done without preliminary scratch studies.

Assuming that with the sensitization studies we have identified certain allergenic foods in a case of presumptive abdominal allergy, the first step in treatment will be the elimination of the offending foods from the dietary. This may be all that is necessary, but sometimes other factors must be considered in the diet. In allergic mucous colitis, first described by the writer in 1922, I have emphasized[4] that by the time the case presents himself for treatment there are usually several factors other than the allergy which require treatment. The mechanical irritation of chronic constipation or from roughage diet, the hyperemia of a chronic diarrhea, repeated insults from chronic catharsis, possibly also secondary infection, all require attention.

Food Diary. If the skin tests are negative or if, after trial, we conclude that all of the allergenic foods have not been discovered, two other methods of study remain. These are the food diary and the trial diet. These have distinct spheres of usefulness. If the symptoms are practically continuous and presumably the offending food is being eaten daily or nearly so, the food diary is not likely to solve the problem. Instead, the patient is placed on a trial diet from which those foods which experience has shown to be frequently allergenic have been eliminated. If, on the other hand, symptoms manifest themselves at intervals of several days, the food diary is employed. (Chart I.) The patient tabulates all substances which pass the lips. Each day he adds any new food at the bottom of the list. In the column for each day he checks all foods eaten on that day. Methods of cooking and food combinations show on the table. It is not sufficient for example to record "eggs." Scrambled eggs and omelets are reported as two entirely different foods. Roast beef and beefsteak are separated. Salads are classified according to all of their constituents.

CHART I.—FOOD DIARY FORM.

NAME_____

Food Diary for five weeks from_____ to_____

Food.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.
Food.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.	S.	M.	T.	W.	T.	F.	S.

Days on which symptoms are manifest are checked. Not infrequently certain foods stand out as being frequently or constantly present on those days or on the preceding day. Sometimes combinations of two foods are suspected. These are then avoided for a period sufficiently long to determine whether they were actually allergenic. At the same time the diary is continued in further search for offending foods.

A record of the foods eaten is not sufficient. On the reverse of the chart the patient keeps a diary of the events of each day. I am indebted to Dr. Alvarez for a most striking example of the value of a record of the events of each day. The case was that of a man in whom food allergy was suspected but in which the usual methods of study had failed to demonstrate the cause. The patient was a railroad man and his run would carry him at intervals to a certain large city. It developed from the study that his attacks would invariably occur either on the day of his visit to the city or on the following day; the attacks had some relationship to his visiting the city. Now he was very fond of cheese and there was a certain restaurant in this city where he could procure a certain brand of cheese which was especially to his liking. This, it developed, was the offending allergen. In such a case the food diary would have failed because cheese was eaten both in the city and elsewhere. The observation that attacks followed trips to the city led ultimately to the discovery that cheese eaten at home was innocuous and that only the special brand mentioned caused trouble.

Trial Diet. We are indebted especially to A. Rowe[5] for the clinical use of the elimination diet, a method which has not yet become popularized but which I have found indispensable in my study of food allergy. Rowe tabulated the frequency of sensitiveness to the different foods in a large number of allergic cases and selected from this table those foods which from experience had been found to be the most infrequently allergenic. These he built up into a series of 5 elimination diets. If after 2 weeks or more on one such diet the patient is not relieved, another is substituted which contains few or none of the foods listed in the first diet but which is still made up of infrequently allergenic foods. He often finds that on one or another of these elimination diets the patient became symptom-free. This is then used as a basic diet and single foods are slowly added to it over a period of weeks. Any new food which is found to produce symptoms is permanently excluded. In this way all of the offending foods may be gradually discovered.

Biologic Food Groups. Until very recently no attempt had been made to classify the vegetable foods biologically as has been so well done with the pollen allergens. The writer has presented such a classification, and his study of food allergens in relation to this grouping has led to some rather interesting observations[6] (Table 1). Those that bear on the subject in hand may be briefly summarized

as follows: Where one member of a biologic food group has been proven to be allergenic to an individual, other members of the same group may cause allergic symptoms, even though their skin-test reaction has been negative. Sometimes a positively reacting member of a group is found to give rise to no symptoms whatsoever, while a negatively reacting member of the same group does cause trouble. If one is sensitive to one member of a group it does not necessarily follow that all other members will produce symptoms. It only indicates the need for caution in the eating of the other members until it has been definitely determined whether they are allergenic or not.

TABLE 1.—THE BIOLOGIC GROUPING OF THE COMMONER VEGETABLE FOODS.

Graminæ	*Chenopodiaceæ*	*Pomaceæ*	*Umbelliferæ*
Wheat	Spinach	Apple	Carrot
Rye	Beet	Pear	Parsnip
Barley	Swiss chard		Parsley
Oat		*Drupaceæ*	Celery
Rice	*Cruciferæ*	Almond	
Corn	Radish	Plum, prune	*Solanaceæ*
	Turnip	Cherry	Potato
Liliaceæ	Rutabaga	Apricot	Egg plant
Onion	Mustard	Peach	Tomato
Garlic	Cabbage		
Asparagus	Kale	*Leguminosæ*	*Cucurbitaceæ*
	Brussels sprouts	Peas	Pumpkin
Polygonaceæ	Kohlrabi	Beans	The squashes
Buckwheat	Cauliflower	Lentil	The melons
Rhubarb	Broccoli	Peanut	Cucumber (pickles)
Juglandaceæ	*Rosaceæ*	*Rutaceæ*	*Compositæ*
Black walnut	Blackberry	Lemon	Salsify (oyster plant)
English walnut	Raspberry	Orange	Chickory
Pecan	Strawberry	Grapefruit	Endive
Hickory			

NOTE.—Vegetable foods not listed are not closely related to other foods.

These observations have a definite application in the formulation of the elimination or trial diet. In the dietaries formulated by Rowe and others different foods appear in the five different diets, but they are sometimes very closely related biologically.

My own trial diet is therefore based not only upon knowledge of what foods rarely give positive skin reactions, but also upon an understanding of the biologic grouping of foods. The occurrence of crossed reaction within biologic groups appears not to be extremely frequent, and diets such as Rowe's will usually suffice, but in the event relief from symptoms is not obtained with them, one should bear in mind that crossed reaction may be responsible for failure, and should take steps to eliminate entire biologic groups rather than individual foods.

In the formulation of my trial diet I have made a study of the frequency of the positive food reactions as I have observed them in the southeastern States and compared it with Rowe's study for the Pacific coast.[7]

From a comparison of these 2 tables I have arranged a base list or foundation list of foods consisting of, first, those foods which are infrequently allergenic and second, foods such as are not closely related genetically to others. (Table 2.) The patient is first tested with the food allergens. Those foods to which he gives positive reactions as well as foods belonging in the same biologic group are then eliminated. This, of course, applies also to the foundation list. Foods which the patient from his own experience has suspected of causing trouble are also customarily eliminated. The remaining, apparently innocuous foods, now form a list from which articles may be selected to be built upon the foundation list, to provide a fairly well-balanced diet. Since the trial diet is rarely used unaltered more than 2 weeks, it need not be perfectly balanced as regards food value. Only one meat and one cereal are added at the beginning, preferably such as are not eaten routinely. The choice is usually between rye, corn and rice among the cereals and lamb and fowl among the meats. Additions are made gradually with the vegetables and, as a rule, all the members of one biologic group are added before proceeding to a new group. If one member of a food group produces symptoms it does not necessarily follow that other members will do likewise, but special watch is made of the effects of other members of the group. As a rule, new foods are added singly and not oftener than one every third day.

TABLE 2.—BASE LIST OF FOODS FOR USE IN THE FORMULATION OF THE TRIAL DIET.

Pineapple	Huckleberry
Mulberry	Cranberry
Fig	Olive
Buckwheat	Sweet potato
Rhubarb	Salsify (oyster plant)
Hazelnut, filbert	Chicory
Chestnut	Endive
Currant	Artichoke
Gooseberry	Sugar
Pistachio nut	Salt
Okra, gumbo	Maple syrup
Tea	Gelatin

It is obvious that Rowe's 5 trial diets may be employed without previous skin testing. If one has gone through all 5 diets and the patient is not relieved, and if we are still reasonably sure that we are dealing with food allergy one should then have recourse to the sensitization test to see if it will shed further light. With the trial diet which I have described, the sensitization test should be done first since the selection of foods for addition to the foundation list will depend in great measure upon the positive reactions observed and their relationship to other members of the food groups.

Discussion. From the preceding it develops that in a case of suspected food allergy the diagnostic survey has really only commenced at the completion of the sensitization studies. Although

food tests as performed today are not over 50 per cent accurate diagnostically, they make the best point of departure at the beginning of the study, for when positive they provide a definite starting point in the formulation of the diet. If their use decreases the amount of subsequent necessary investigation by 50 per cent or even by but 25 per cent, they are well worth employing. With the completion of these tests the results are correlated with the patient's dietary history and a tentative diet is arranged. Any allergic diet must be followed rigorously for at least two weeks before we can be certain of results. If, after this, symptoms persist, we may have recourse to the food diary, where symptoms are intermittent or the trial or elimination diet where they are more constant, or indeed, a combination of both. For example, after a patient has been placed on the trial diet we will often have him keep a food diary at the same time. The limitation of his diet facilitates the study of the food diary.

Finally, I would emphasize that it is not sacrilege for the allergist to employ other therapeutic measures than purely allergic, directed against the other related nonspecific factors such as intestinal stasis, bile tract infection, ulcer, diabetes, tuberculosis, etc. In the treatment of gastrointestinal allergy the gastroenterologist and the allergist stand on common ground and each should avail himself of the therapeutic advantages made possible by the other.

REFERENCES.

1. Balyeat, Ray M.: Allergic Migraine (in press).
2. Menkin, Valy: Studies on Inflammation. IV. Fixation of Foreign Protein at Site of Inflammation, J. Exp. Med., 1930, **52**, 201.
3. Auer, John: The Influence of Systemic Changes on Local and Tissue Reactions, Proc. Soc. Exp. Biol. and Med., 1919, **17**, 93.
4. Vaughan, Warren T.: Diseases Associated with Protein Sensitization, Virginia Med. Monthly, 1922, **49**, 316; Allergic Factor in Mucous Colitis, South. Med. J., 1928, **21**, 894.
5. Rowe, Albert H.: Food Allergy, J. Am. Med. Assn., 1928, **91**, 1623.
6. Vaughan, Warren T.: Food Allergens. I. A Genetic Classification with Results of Group Testing, J. Allergy, 1930, **1**, 385.
7. Vaughan, Warren T.: Food Allergens. II. Trial Diets in the Elimination of Allergic Foods, J. Immunol., 1931, **20**, 313.

SYDENHAM'S CHOREA.

By R. W. Waggoner, M.D., Sc.D.,

ASSISTANT PROFESSOR OF NEUROLOGY, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL; ASSISTANT NEUROLOGIST, UNIVERSITY HOSPITAL, ANN ARBOR, MICH.

(Read before the University of Michigan Pediatric Society, November 14, 1930.)

Chorea is a general term covering a number of disease entities. This paper will deal only with Sydenham's chorea, a disease which was first described by Sydenham in his "Schedula Monitoria"

in 1686 and later in his "Processus Integri" in 1693. Both of these works gave a very brief but accurate account of the disease as it is now described. With your permission I shall quote from the "Processus," Chapter XVI, on "St. Vitus' Dance:"; "This is a kind of a convulsion which attacks boys and girls from the tenth year to the time of puberty. It first shows itself by limping or unsteadiness in one of the legs which the patient drags. The hand cannot be steady for a moment; it passes from one position to another by a convulsive movement however much the patient may strive to the contrary. Before he can raise a cup to his lips he makes as many gesticulations as a mountebank, since he does not move it in a straight line, but has his hand drawn aside by spasms until by some good fortune he brings it at last to his mouth. He then gulps it up at once so quickly and so greedily as to look as if he were trying to amuse the lookers-on."

The treatment used by Sydenham might also be of interest. The patient was bled one day some 8 ounces, the next day he was given a concoction of black cherry water, aqua epileptica Langii, venus treacle, and liquid laudanum. The bleeding and catharsis were alternated daily for several days, or as long as the patient's physical condition showed that he was able to stand the treatment. On the days when there was no purging the patient was given a very complex shotgun prescription. Plasters were oftentimes applied to the sole of the foot to guard against relapse. It was also advised that the patient be bled and purged for a few days each year at about the time of the expected onset of the condition. It is interesting to note that Sydenham also suggested that the above treatment might be of value in epilepsy of adults, but added that he had not given it a trial. Since the time of Sydenham many different types of treatment have been suggested for chorea, however, the treatment used at the present time is but slightly more specific than that suggested by Sydenham.

The disease is also spoken of as St. Vitus' Dance. Toward the end of the 14th century a curious mania developed in Germany, the individual so affected performing a wild dance which had the appearance of a person "possessed of the Devil." St. Vitus at that time had considerable fame as a protector against all kinds of sickness but particularly those supposedly due to afflictions by the Devil. Since the movements of Sydenham's chorea resembled to some extent the movements of these people, it came to be called St. Vitus' Dance.

Etiology. At the present time there is no commonly accepted specific etiology for Sydenham's chorea. It is generally supposed that infection of some sort may be a precipitating factor. There seems to be without much doubt a predisposition on the part of the patient to the development of the disease. This predisposition, or hereditary factor, may be dependent upon an inferior integration

of the psychomotor cerebellar mechanism. This is often seen in children who never develop chorea; we say that the child is in the so-called awkward age. In children who have such a predisposition toward the development of chorea we need only to postulate a minor infection to disturb the normal integration of motor characteristics.

The infections which are particularly prone to precipitate the development of chorea are usually of the streptococcic type, such as scarlet fever, acute streptococcic tonsillitis, and acute rheumatic infections. In addition, many of the other children's diseases may serve as the secondary causative agent. It is remarkable how many of the children in this series had a history of whooping cough, measles and chickenpox, while diphtheria and scarlet fever occurred only occasionally. Pneumonia was recorded in a number of instances. It seems of particular interest to note that in the whole series there are recorded only five cases of tonsillitis, and in 2 of these the tonsils had been removed before the onset of chorea. The importance of tonsillitis as a factor in chorea has also been minimized by a number of other authors. Comparatively few cases had a history of acute rheumatic fever, yet a relatively large percentage of these showed physical signs of endocarditis.

The "theory of infection" as a cause for chorea is not new. Todd, in 1840, believed chorea to be rheumatic in origin. Wilson, in 1843, attributed chorea, not to the nervous system, but to "morbid blood" affecting the muscular system. Kirkes, 1863, and Hughlings Jackson, 1869, believed chorea due to showers of minute emboli projected into the cerebral vessels causing minute thrombi. Jackson located the seat of the lesion in the nerve tissues near the corpus striatum. Broadbent, in 1869, stated that he felt chorea was a symptom rather than a disease and could not be referred to any single pathologic lesion. In 1889 Maragliano believed that chorea was the result of a toxic infectious process, thus originating the so-called toxic infectious theory of the disease.

The relation of rheumatic fever to chorea has been variously estimated. Some feel that it is the chief exciting cause of chorea, while others consider that there is little more than a coincidental relationship between them. In this series it is interesting to note that rheumatic fever was noted either during the course of the disease or before the onset of the movements in about 33 per cent of the cases, while in an additional 15 per cent some evidence of cardiac disturbance was noted. This makes a total of approximately 50 per cent in which there was evidence of rheumatic fever or cardiac involvement. However, in a number of these cases an acute infection preceded the development of symptoms whether these symptoms were of acute rheumatic fever or chorea. The most common infection seems to have been either scarlet fever or measles, or both.

All cases but one presented either a history or physical evidence

of some infectious disease or of acute infection which preceded by a short period the onset of symptoms of chorea. The one exception had an impacted tooth, the removal of which was followed by a rapid disappearance of choreiform movements. Those cases showing evidence of rheumatic fever are included as cases of infectious disease. Various other causative factors have been suggested; *e.g.*, a number of authors have remarked upon the importance of oral infection as a precipitating factor, perhaps even as the cause of choreic movements, and they cite cases in which such infection has been removed and has resulted in an almost immediate cure. Impacted teeth have likewise been blamed, the removal of which results in miraculously quick cures. In 1928 an author claimed to have cured a case of sciatica by injection of the nasal ganglion with alcohol, and by the same means he secured an equally remarkable cure of chorea. We find cases reported in which choreic movements have subsided immediately after the patient had been given a vermifuge.

Too little significance has been attached to the psychic factor in the production of chorea. Many cases, perhaps those predisposed, seem to be precipitated into an acute attack by a fright or other violent emotional upset. In these cases a complete examination oftentimes reveals no evidence of an organic factor which might account for the symptoms.

Age and Sex Incidence. Chorea is most commonly seen, as was originally described by Sydenham, between the ages of 10 and 15 years. It may occur as early as 5 years and as late as 20 or more. It is essentially, however, a disease of childhood. Females seem more prone to the disease than males. In the literature the ratio is given as 3 to 1, or 2 to 1. In this series of 125 patients, although not sufficiently large for statistical value, the ratio is about 2 females to 1 male. As to race incidence there seemed to be little or no choice, the American or mixed stock showing the highest percentage, the Irish being second with about 23 per cent, Hebrews with approximately 21 per cent, while Hungarian and Italian children each constituted about 8 per cent of the group studied. There was one pure negro child with the disease. This is interesting because a fairly large percentage of the patients coming to the clinic during the period this work was being carried on were negroes, and so the finding of only one colored child with chorea is perhaps rather surprising. It is perhaps worth while to note that there is a seasonal variation in the disease, its first occurrence being in the spring or fall. Recurrences likewise usually appear at these same periods of the year.

Symptomatology. Sydenham's chorea is characterized by irregular, involuntary, jerky, spasmodic movements which are fairly rapid and of a comparatively wide range. The degree of involvement is extremely variable, being from only one or two muscle

groups to practically the entire body. In some cases there may be noted only twitching, purposeless, jerklike movements of the face, usually on one side, or there may be similar movements involving a finger, hand, all of one extremity, or perhaps half of the body, while in some cases the whole body may be involved in this hyperkinesis. Most patients have involvement of one side first and in many cases the disease remains unilateral. Bilateral involvement, however, is not uncommon. When this occurs the arms and legs are seemingly poorly controlled and are swung about in a wobbly, awkward fashion. In severe cases walking is usually absolutely impossible. There may be involvement of the respiratory system, making the breath come in gasps and groans; the patient may have difficulty in talking. In the milder cases the movements usually cease during sleep, while in the more severe ones the movements may be continuous. In the paralytic types of chorea there may be hemiparesis with a hemiplegic type of gait, a dragging of the extremity on the affected side and inability to use that extremity. The patient in attempting to drink from a glass may eventually be able to get the fluid to his mouth, but is more likely to drop the container. One often gets a history of the child being punished by his parents for being careless, breaking dishes, and the like.

The patient frequently presents mental symptoms as well as the motor symptoms described above. These may be spoken of as periods of emotional instability, fretfulness, peevishness, and unreasonableness. The little patient is tearful, cries at the slightest provocation, is difficult to manage, and seems almost unable to remember. Frequently his sleep is disturbed by horrifying, unpleasant dreams, the content of which he is rarely able to reproduce. There is often a rather characteristic facial expression, the so-called choreic facies. This is best described as an expression of wistfulness. In some cases the loss of memory may be marked and may be associated with deafness, confusion and disorientation. It is unfortunate that in many of these cases the parents fail to realize the seriousness of the disease with which their child is afflicted and for the many little peculiar mental twists, emotional and physical characteristics the child is scolded or punished. This, of course, simply serves to accentuate the symptoms present. It is unfortunate, indeed, that parents do not realize these facts before they have increased the child's disability by ill-advised scolding and punishment.

On examination one finds a diminution and sometimes an absence of the tendon reflexes. They are quite often variable in the same patient. Signs of pyramidal involvement are not infrequent. In some cases there is a definite tendency toward hypotonicity, particularly on the side most affected. The more important signs, however, are those of incoördination of movement, such as adiadochokinesia and asynergia. Such signs are, of course, more prominent on the affected side and are particularly noticeable in those cases

in which there is hypotonia. The patient is absolutely incapable of synergising the normal motor functions and particularly is he unable to carry out complicated associated movements. The apparent muscle weakness which is so frequently noted does not seem to be a true muscle weakness, but rather the result of the continuous movement, of the hypotonia, and of the incoördination.

Sensory symptoms in chorea are comparatively infrequent. Occasionally, but very rarely, the patient will complain of pain and these cases have been described as "painful chorea." Objective sensory signs have not to my knowledge been described.

Some cases of chorea manifest a fever of varying degree, but in most patients examined at the clinic the acute symptoms of infection have disappeared and the temperature has returned to normal, so that it is rare in the usual run of clinic cases to find a rise in temperature.

Blood Findings. The blood chemistry is in most cases essentially normal. The white blood cell count may be moderately increased. The blood Wassermann is not infrequently positive, particularly in chronic cases. Chronic cases seem often to be associated with hereditary syphilis. The spinal fluid may show a pleocytosis of moderate degree.

Pathologic Anatomy. The pathology of the average case of chorea minor is not much better known than its etiology, since very few cases ever come to autopsy. Those cases which are fatal are usually so acute and present such an exaggeration of symptoms, that it is doubtful whether we should consider the lesions found in these cases to be those of the usual or average case. It is usually considered, however, to be a type of encephalitis involving both the cortex and basal ganglia, but more particularly the basal ganglia region with the greatest involvement in the corpus striatum. There has been described dilatation of the capillary blood vessels and a type of perivascular infiltration with punctate hemorrhages which eventuate in a type of granular degeneration. In a recently reported case showing choreic symptoms on one side of the body, a postmortem of the brain showed destruction of the corpus Luys with involvement of the descending fibers on the opposite side. This author concludes that the impulses for the movements seen in chorea arise at a lower level than the corpus Luys, and he goes so far as to state that the choreic movements do not appear providing the corpus Luys is intact. In some cases with coincidental endocarditis there has been noted chromatolysis of practically all cells of the central nervous system with swelling and eccentric displacement of the nuclei, also curious fatty deposits in the large cells of the motor cortex and the small cells of the palladium. Fat has also been demonstrated in the perivascular spaces. In some cases rheumatic nodules have been described in the brain. It is, I believe, fairly safe to consider that the pathology of chorea is that of a generalized

encephalitis which involves, predominantly the basal ganglia, and particularly the striatum. We may theorize somewhat and say that the movements of chorea are the result of the removal of the inhibitory influence of the higher physiologic levels with consequent overfunction of lower motor areas. Obviously, since the destruction is rarely if ever complete, the inhibitory influence is not completely removed and the movements retain some suggestion of normality.

Treatment. The multiplicity of treatments suggested for Sydenham's chorea is evidence enough that most of them are unsatisfactory. The first and most important dictum in the successful treatment is rest, absolute rest in bed with isolation of the individual from all possible stimuli, particularly social stimuli. This means mental as well as physical rest and therefore reading, toys, and the like are contraindicated. In addition to the absolute rest, a good nourishing diet with plenty of vegetables but with a low meat ration is essential. The second important dictum in the schedule of treatment is the elimination of foci of infection. Many authors favor the elimination of these foci, such as septic tonsils and septic teeth, immediately upon admission of the patient to the hospital. However, it seems to me that it is better and much more satisfactory to the patient to wait until the movements have either ceased or are much decreased. If at the time of admission there is a fever, the elimination of foci should wait until the temperature has returned to normal. In support of the above I would point out the large amount of work done showing that removal of tonsils, teeth, and other foci has apparently not changed the course of the disease in the slightest. In addition, if the patient at the time of admission is particularly easy to disturb emotionally, early operative procedures may cause a serious psychic shock to the patient.

Sera of various types have been suggested in the treatment of chorea. Some authors advocate a serum made from the patient's own blood and given intraspinally. Others, *e.g.*, Rosenow and Small, have developed sera which are supposed to be specific for the disease. The authors of these various treatments report a remarkably high percentage of cures but unfortunately their results have not been substantiated by other workers in the field. Cases of chorea have been reported as recovering after lumbar puncture, the recovery being explained on the basis of relief of pressure on the brain. There have been reported some cases of chorea treated by epinephrin which showed marked improvement. However, other authors trying to substantiate these results have been unable to report similar findings.

Foerster's theory is that each movement is composed of two constituents, a corticospinal and a corticothalamopallidal component, the latter component being constantly inhibited by the striatum. A lesion of the small cells of the striatum or striopalladial fibers

would then give an unequal inhibition and result in an ataxia of movement. Working on this hypothesis Marinesco, Sager, and Diniochiotu have elaborated a treatment by the use of sodium luminal and magnesium sulphate which is said to give good results, since sodium luminal and magnesium sulphate inhibit the action of the diencephalon and the mesencephalon. The luminal treatment consists in subcutaneous injections twice daily of 0.22 gram of sodium luminal over a period of 20 to 25 days. At the same time the patient is given magnesium sulphate intraspinally, in a dosage of 8 mg. per kilogram of body weight. These injections are likewise repeated every day for 26 days. I have had no experience with this type of treatment.

Some authors believe that the course of chorea is shortened by the use of arsenic in various forms, the favorite form, of course, being Fowler's solution. Personally, I do not believe that Fowler's solution influences the course of the chorea in any way.

In those cases associated with rheumatic involvement it is usually of value to include salicylates in the treatment.

A treatment which has received a great deal of attention lately is the nirvanol treatment, nirvanol being phenyl-ethyl-hydantoin. A number of authors have reported the use of this drug with very beneficial results. They feel that improvement is more marked in the more severe cases. In some of the milder cases it seems to have little or no influence. The drug is reported as being dangerous in that it may produce a leukopenia with eosinophilia, or even agranulocytosis. It is not to be administered over a period of more than 10 days. The dosage in young children is 5 grains a day; in older children, 10 grains a day, to be given over a period of from 7 to 9 days, or until the development of the so-called nirvanol sickness. On about the seventh day there usually appears a fever which reaches its maximum on the ninth day and subsides on the eleventh day. The drug is discontinued when the fever or a rash appears. Usually on the ninth day a reddish-brown maculopapular eruption appears on the thighs, wrists and abdomen. In 1 or 2 days it becomes a generalized urticaria-like eruption. There may be an associated intense pruritus. The leukopenia and eosinophilia are seen in most cases, agranulocytosis and other ill effects, such as hemorrhagic nephritis, occurring but rarely. No work has been done on the localization of the drug in the central nervous system, but it is supposed to act on the thalamus and corpus striatum. In one series the duration of the disease in the control cases averaged 115 days, while the nirvanol treated cases averaged 31 days.

Conclusions. Sydenham's chorea is a disease of childhood, 80 per cent of the cases occurring between the ages of 5 and 15 years. It does, however, occur in younger and in older children. The incidence in females is twice that in males. It is a disease characterized by irregular, involuntary, jerky, spasmodic, moderately

quick movements associated with some depression of the tendon reflexes and possibly evidence of involvement of the pyramidal pathways. The disease is practically always associated with mental symptoms during the acute stage. These mental symptoms are in effect a variance of the normal personality reactions. These variations may be accentuated rather markedly by ill-advised handling and treatment, particularly in the home before the disease is recognized. The disease most likely occurs in individuals in whom there is a predisposition which is the result or cause of a poor integration of the cerebrocerebellar motor mechanism.

Pathologically it is a type of encephalitis characterized by involvement of both the cortex and basal ganglia, but particularly of the corpus striatum and perhaps the corpus Luys.

The most essential part of the treatment of chorea is absolute mental and physical rest, best obtained by the removal of the patient from his home and placing him in an institution where his environment can be properly controlled. The multiplicity of treatments suggested are evidence of their inadequacy. The removal of the foci of infection is important but should be delayed until the child has become accustomed to his new environment, until there has been a diminution in the movements exhibited, and until the fever which the patient may have has disappeared. Infections such as acute rheumatic fever, acute tonsillitis, acute nephritis, and scarlet fever, are coincident or precipitating factors and are not the primary causes of Sydenham's chorea.

BIBLIOGRAPHY.

1. Ashby, Hugh T.: Treatment of Chorea by Nirvanol, Arch. Dis. Childhood, 1930, **5**, 42.

2. Burr, C. W.: A Study of the Last 515 Cases of St. Vitus' Dance Treated at the Clinics of the Orthopedic Hospital and Infirmary for Nervous Diseases, Atlantic Med. J., 1924–1925, **28**, 568.

3. Bird, Hiram: The Nasal Ganglion and Chorea, Arch. Otol., 1928, **7**, No. 3.

4. Charney, Charles: Two Cases of Chorea Treated by Small's Anti-serum, Med. J. and Rec., 1929, **129**, 99.

5. Cassoute, Raybaud, and Montus, Mm.: Chorres de Sydenham gueries par une ponction lombaire, Soc. de ped. de Paris., 1927–1928, **25–26**, 49.

6. Duzar J.: Hormon behand Lung der Chorea minor, Klin. Wchnschr., **153**, No. 5.

7. Epstein, J.: Chorea: Its Genesis and Its Classification, Arch. Pediat., 1930, **47**, 119.

8. Foerster, O.: Quoted from Marinesco, G., Sager, O., and Denischiotu, G. T.

9. Gerstley, Jesse R.: Chorea: Some Clinical Observations with a Suggestion for Further Study, Illinois Med. J., 1928, **54**, 117.

10. Gerstley, Jesse R.: Chorea, Am. J. Dis. Childhood, 1927, **33**, 602.

11. Graham, Stanley: Arsenic in the Treatment of Chorea, Arch. Dis. Childhood, 1928, **3**, 206.

12. Hartzell, Ray. H., and Cunningham, John: Phenylethylhydantoin in Treatment of Sydenham's Chorea (Nirvanol), Am. J. Dis. Childhood., **39**, No. 6, 1205.

13. Kaiser, A.D.: Incidence of Rheumatism, Chorea and Heart Disease in Tonsillectomized Children, J. Am. Med. Assn., 1927, **89**, 2239.

14. Karelitz, Samuel: The Treatment of Chorea Minor with Epinephrine, J. Am. Med. Assn., 1927, **89**, 1603.

15. Kundratitz, Karl: Der thyreotoxische Symptomenkomplex bei Chorea minor, Ztschr. f. Kinderh., 1927, **43**, 658.
16. Lhermitte, J., and Pagniez, Ph. Mm.: Les lesions cerebrales de la choree de Sydenham a forme aigue, Arch. de méd. d. Enf., 1930, **33**, 156.
17. Letelier Ladislao Iabra: De l'amygdalectomie et de l'adenotomie dans le traitément de la choree de Sydenham, Rev. de laryngol., d'otol. et de rhinol., 1930, **51**.
18. Marinesco, G., Sager, O., and Denischiotu, G. T.: Sur le traitément de la choree par le luminal et de sulpte de magnesium avec considerations sur la physiopathologie de la choree, Ann. de méd., 1930, **27**, 237.
19. Martin, J. P.: Chorea, The Symptoms Which Result from Injury to the Corpus Luysii, Lancet, 1928, **2**, 315.
20. Poynton, J., and Schlesinger, B.: Treatment of Chorea by Nirvanol, Lancet, 1929, **2**, 267.
21. Ritenour, J. P.: Chorea Caused by Impacted Teeth, Pennsylvania Med. J., 1928–1929, **32**, 773.
22. Stephens, G. A.: A Superficial Dorsal Reflex in Chorea, Med. Rev. of Rev., **36**, No. 10.
23. Thomson, D., and Thomson, R.: An Historical Survey of Researches on the Rôle of Streptococci in Chorea, Ann. Pickett-Thomson Res. Lab., **4**.
24. Vastine, A. B.: Certain Etiologic Factors in Chorea, Atlantic Med. J., 1928, **31**, 564.
25. Wegman, M. E.: Chorea and Athetosis, Yale J. Biol. and Med., 1930, **2**, 269.
26. Wilson, S. A. K.: Die Pathogenese der unwillkürlichen Bewegungen mit besonderer Berücksichtigung der Pathologie und Pathogenese der Chorea, Deutsch. Ztschr. f. Nervenh., **107**, **108**.
27. Waggoner, R. W.: Personality Studies in Children with Particular Reference to Chorea Cases, Thesis for Sc.D., University of Pennsylvania.
28. Warner, W. C.: A Study of the Basal Metabolic Rate in a Series of Cases of Chorea, Guy's Hosp. Rep., 1930, **80** (vol. **10**, 4th ser.).
29. Williams, J. C.: Two Cases of Chorea Treated by Small's Anti-serum, Med. J. and Rec., 1929, **129**, 100.
30. Ziegler, L. H.: The Neuropathological Findings in a Case of Acute Sydenham's Chorea, J. Nerv. and Ment. Dis., 1927, **65**, 273.

CREATINURIA IN HYPERTHYROIDISM.*

By Edwin J. Kepler, M.D.,
DIVISION OF MEDICINE,
AND
Walter M. Boothby, M.D.,
SECTION ON CLINICAL METABOLISM, THE MAYO CLINIC, ROCHESTER, MINN.

Comparatively few clinical studies of the disturbances in the creatin-creatinin metabolism in hyperthyroidism are recorded in the literature.

Shaffer (1907) was the first to point out that creatinuria occurred in exophthalmic goiter. He found creatin in the urine in 8 of 12 cases studied. In some cases the creatin excreted exceeded the creatinin excreted. The latter was found always to be very low in

* Abstract of thesis submitted by Dr. Kepler to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1929. Submitted for publication January 21, 1931.

amount when the creatinin coefficients were calculated. Denis and Minot (1917), and Denis and Kramer (1917) presented data suggesting that the amount of creatin excreted in cases of exophthalmic goiter was dependent on the intake of protein, and that it was increased by a diet high in protein and decreased or even abolished by a diet low in protein. Denis and Minot (1919) were unable to reduce the degree of creatinuria in exophthalmic goiter by giving sodium bicarbonate by mouth. From this they concluded that acidosis was not responsible for creatinuria. Palmer (1927), in a preliminary report, stated that the creatinuria of exophthalmic goiter could be markedly diminished by the administration of iodin. A complete report of this work was published by Palmer, Carson and Sloan in February, 1929. Included in the reports were 11 cases of adenomatous goiter with hyperthyroidism and 32 cases of exophthalmic goiter. It was found that "in all cases excreting appreciable amounts of creatin in the urine there is a marked diminution of the creatinuria following the administration of iodin," and that "the influence of iodin on the creatinuria is usually accompanied by a fall in basal metabolism, but not always."

After the publication of the report by Palmer, a similar study was started in the metabolism laboratories of The Mayo Clinic.

Method of Study and Results. Creatin was determined by the method of Benedict, and creatinin by the method of Folin. All analyses were made in duplicate. Both creatin and creatinin were calculated and expressed as nitrogen. The cases were divided into 3 groups.

Group 1. This group served as a control and consisted of 274 patients (76 males and 198 females) from whom samples of urine were taken. These patients represented the general run of those who register at the clinic, with the exception that patients with hyperthyroidism were excluded. The urine was examined only for the presence or absence of creatin, in order to determine the frequency of creatinuria in conditions other than hyperthyroidism. Since in this group the specimens of urine were not collected over a period of 24 hours, all calculations in the data were made on the basis of 1 liter of urine. Unless the amount of creatin calculated as nitrogen exceeded 0.02 gm. in each liter, the urine was considered to be free of creatin. When the calculated amount of creatin nitrogen was more than 0.02 gm. but less than 0.04 gm. the urine was considered to contain traces of creatin; it was considered to contain definite amounts when the calculated nitrogen exceeded 0.04 gm. but was less than 0.1 gm., and marked amounts when the calculated nitrogen exceeded 0.1 gm. In some instances when creatin was found only in traces probably creatin was actually present in the urine; in other instances creatin was probably absent, and the amount determined represented unavoidable technical errors due to the limitations of the method.

Traces of creatin were found in the urine of 7 of the 76 male patients (9 per cent). Only 1 patient showed more than a trace; this was a boy aged eleven years.

Traces of creatin were found in the urine of 17 of the 198 female patients (9 per cent); it was found in definite amounts in 13 patients (7 per cent), and in marked amounts in 14 patients (7 per cent), making a total of 23 per cent including those showing traces, or 14 per cent excluding those showing traces. The creatinuria in these women occurred in definite or marked amounts in the following conditions: arthritis, 4 cases; cholecystitis, 3 cases; constipation, 1 case; hypertension, 2 cases; indeterminate, 2 cases; intraocular tumor, 2 cases; gumma of leg, 1 case; migraine, 2 cases; normal woman, 1 case; neurosis, 2 cases; obesity, 2 cases; pituitary tumor, 1 case; pregnancy, 2 cases; scleroderma, 1 case, and uterine fibromyoma, 1 case. In some instances the creatinuria may possibly have been a concomitant of the disease; in others, it represented merely the not infrequent creatinuria occurring in women.

Group 2. This group consisted of 154 patients taken at random from those treated in the hospital for goiter. Nine of these patients did not have hyperthyroidism. The group included cases of exophthalmic goiter, adenomatous goiter with hyperthyroidism and adenomatous goiter without hyperthyroidism. Many of the patients had been treated with iodin before admission to the hospital. The urine in these cases was examined once or twice immediately after admission, to determine the presence or absence of creatin. As in Group 1, creatin was not considered to be present unless the amount, calculated as nitrogen, exceeded 0.02 gm. in each liter of urine. Tables 1 and 2 show the results obtained in this group. One hundred fifteen patients had exophthalmic goiter; 39 of these were males. Thirty patients had adenomatous goiter with hyperthyroidism; 5 of these were males. Nine patients had adenomatous goiter without hyperthyroidism; all were females.

Table 1 shows that of 25 untreated female patients with exophthalmic goiter, 21 (84 per cent) had demonstrable creatinuria and that of 8 men similarly affected, all had creatinuria. In the entire series of 115 patients with exophthalmic goiter 60 per cent of the males and 62 per cent of the females showed the presence of creatin, regardless of the fact that nearly two-thirds had been given iodin for several days and that some had received iodin for as long as a month. The incidence of creatinuria was less in those patients who were under treatment with iodin, although the decrease cannot be said to be closely related to the length of time of administration.

The incidence of creatinuria in cases of adenomatous goiter with hyperthyroidism is shown. Two of the 5 males (40 per cent) had creatinuria and 17 of the 25 females (68 per cent) had creatinuria. Creatinuria was demonstrated in 19 (63 per cent) of the total number, an incidence slightly more than that occurring in the entire

group of exophthalmic goiter but not as high as in the untreated cases of exophthalmic goiter.

TABLE 1.—INCIDENCE OF CREATINURIA IN GROUP 2.

	Exophthalmic goiter; administration of compound solution of iodin, days.							Adenomatous goiter.	
	None.	1 to 3.	4 to 7.	7 to 14.	14 to 30.	More than 30.	Total.	With hyperthyroidism.	Without hyperthyroidism.
Males:									
With creatinuria	8	3	5	2	1	4	23	2	
Without creatinuria	...	3	6	4	3	...	16	3	
Per cent with creatinuria	100	50	45	33	25	100	60	40	
Females:									
With creatinuria	21	10	7	5	2	2	47	17	1
Without creatinuria	4	2	10	5	5	3	29	8	8
Per cent with creatinuria	84	80	41	50	30	40	62	68	11
Total:									
With creatinuria	29	13	12	7	3	6	70	19	
Without creatinuria	4	5	16	9	8	3	45	11	
Per cent with creatinuria	87	72	43	44	27	67	61	63	

The fact that in exophthalmic goiter the incidence of creatinuria was 61 per cent, and in adenomatous goiter with hyperthyroidism, 63 per cent, while in the control group it was only 9 per cent in males and 23 per cent in females, indicates that creatinuria can be considered as a fairly common and characteristic phenomenon of hyperthyroidism. The incidence of creatinuria in females with adenomatous goiter without hyperthyroidism was only 11 per cent.

A comparison of the duration of the disease with the incidence of creatinuria in untreated exophthalmic goiter was made, but on account of the irregularity of the results and the relatively small number of cases conclusions could not be drawn. It was evident that age is probably not a determining factor in the production of creatinuria in adult patients with exophthalmic goiter. Palmer, likewise, did not find correlation between the excretion of creatin and the age of the patients in his cases of exophthalmic goiter.

In Table 2 the basal metabolic rate is compared with the intensity of the creatinuria in cases of exophthalmic goiter in which treatment was not given. It is seen that there is not a strict parallelism between the basal metabolic rate and the amount of creatin excreted; yet it is equally evident that the amount of creatin excreted by a group of patients whose metabolic rates were very high was much greater than in a group whose metabolic rates were low.

GROUP 3. This group consisted of 10 patients who had frank exophthalmic goiter. Daily 24-hour specimens of urine from the

time of admission to the time of dismissal of each patient were examined. The routine treatment for exophthalmic goiter employed at the clinic was given to all of these patients. The diet was not restricted to food free from creatin. Compound solution of iodin was given in doses of 30 minims daily, except in one instance (Case 1, Table 3) in which 100 minims were given daily for the first 4 days. The purpose of this part of the study was to determine the effect of iodin on the excretion of creatin. Nine of the 10 patients underwent thyroidectomy and, incidentally, the effect of thyroidectomy on excretion of creatin was determined in these 9 cases. The patients in this group were not under such close supervision as is necessary for conducting complete metabolic experiments, and the specimens of urine obtained were somewhat irregular and incomplete. Because of this irregularity the percentage of the total creatinin nitrogen which appeared as creatin nitrogen is of more significance than the absolute amounts of these substances. The failure of the patient to empty the bladder at a stated time each day and the incompleteness of some of the specimens of urine undoubtedly accounts, in large part, for the variations in the output of preformed creatinin nitrogen.

TABLE 2.—RELATION OF INITIAL BASAL METABOLIC RATE TO AMOUNT OF CREATIN EXCRETED IN EXOPHTHALMIC GOITER NOT TREATED WITH IODIN (GROUP 2).

Sex.	Basal metabolic rate, per cent.	Creatin in each liter, gm.	Sex.	Basal metabolic rate, per cent.	Creatin in each liter, gm.
M	+13	0.04	F	+44	0.00
M	+35	0.05	F	+46	0.24
M	+44	0.03	F	+47	0.11
M	+47	0.03	F	+51	0.21
M	+56	0.04	F	+51	0.06
M	+68	0.20	F	+54	0.07
M	+83	0.28	F	+56	0.08
M	+110	0.11	F	+57	0.00
F	+8	0.10	F	+59	0.09
F	+25	0.01	F	+59	0.11
F	+26	0.30	F	+61	0.03
F	+28	0.09	F	+63	0.11
F	+29	0.17	F	+63	0.24
F	+32	0.07	F	+68	0.25
F	+37	0.03	F	+68	0.12
F	+40	0.00	F	+88	0.14
F	+42	0.04			

The data presented in Table 3, from 4 representative cases, confirm the observation of Palmer that as patients with exophthalmic goiter improve following the administration of iodin, a decrease in the amount of creatin excreted occurs. Generally the decrease was noticeable within the first 3 days and was marked by the end of a week, when creatin had practically disappeared from the urine. In 5 of 9 cases the creatin appeared for a few days following thyroidectomy, even with the continued administration of iodin. In 3

patients the amount of creatin excreted postoperatively exceeded the initial amount excreted before iodin was given. It is not known whether the postoperative creatinuria bears any relation to the severity of the postoperative reaction.

TABLE 3.—REDUCTION OF CREATINURIA IN EXOPHTHALMIC GOITER FOLLOWING THE ADMINISTRATION OF COMPOUND SOLUTION OF IODIN (GROUP 3).

Case.	Age.	Sex.	Diagnosis.	Date.	Basal metabolic rate, per cent.	Total creatinin nitrogen, gm.	Preformed creatinin nitrogen, gm.	Creatin nitrogen, gm.	Creatin nitrogen in amount of total creatinin nitrogen, per cent.
1	56	F	Exophthalmic goiter patient in crisis	4–7*	+64	0.26	0.10	0.16	62
				4–8	....	0.29	0.12	0.17	59
				4–9	....	0.29	0.12	0.17	59
				4–10	....	0.25	0.13	0.12	48
				4–11	....	0.29	0.19	0.10	34
				4–12	....	0.21	0.16	0.05	24
				4–13	+43	0.28	0.18	0.10	36
				4–14	....	0.16	0.15	0.01	6
				4–15	....	0.20	0.20	None	None
				4–16	....	0.20	0.20	None	None
				4–17	+34	0.13	0.13	None	None
				4–18	....	0.12	0.12	None	None
				4–19	....	0.13	0.13	None	None
				4–20	....	0.21	0.21	None	None
				Returned home for 10 days					
				4–30	+52	0.10	0.10	None	None
				5–1	....	0.16	0.16	None	None
				5–2†	....	0.17	0.17	None	None
				5–3	....	0.22	0.16	0.06	27
				5–4	....	0.29	0.23	0.06	21
				5–5	....	0.49	0.25	0.24	49
				5–6	....	0.25	0.15	0.10	40
				5–7	....	0.25	0.15	0.10	40
				5–8	....	0.18	0.18	None	None
				5–9	....	0.19	0.19	None	None
				5–10	....	0.24	0.24	None	None
2	33	F	Exophthalmic goiter (patient moderately ill)	4–12	+49				
				4–17*	+45				
				4–18	....	0.37	0.20	0.17	46
				4–19	....	0.33	0.20	0.13	39
				4–20	....	0.28	0.19	0.09	32
				4–21	....	0.25	0.16	0.09	36
				4–22	+32	0.31	0.22	0.09	29
				4–23	....	0.31	0.22	0.09	29
				4–24	....	0.25	0.22	0.03	12
				4–25	....	0.25	0.22	0.03	12
				4–26†	....	0.24	0.19	0.05	21
				4–27	....	0.21	0.16	0.05	24
				4–28	....	0.44	0.19	0.25	57
				4–29	....	0.35	0.20	0.15	43
				5–1	....	0.30	0.24	0.06	20
				5–2	....	0.18	0.18	None	None
				5–3	....	0.15	0.15	None	None
				5–4	....	0.19	0.19	None	None

* Administration of iodin started. † Thyroidectomy performed.

TABLE 3.—REDUCTION OF CREATINURIA IN EXOPHTHALMIC GOITER FOLLOWING THE ADMINISTRATION OF COMPOUND SOLUTION OF IODIN (GROUP 3.)—*Continued.*

Case.	Age.	Sex.	Diagnosis.	Date.	Basal metabolic rate, per cent.	Total creatinin nitrogen, gm.	Preformed creatinin nitrogen, gm.	Creatin nitrogen, gm.	Creatin nitrogen in amount of total creatinin nitrogen, per cent.
3 . .	50	F	Exophthalmic goiter (patient moderately ill)	4–17*	+46				
				4–18	....	0.35	0.30	0.05	14
				4–19	....	0.21	0.18	0.03	14
				4–20	....	0.36	0.27	0.09	25
				4–21	....	0.32	0.17	0.15	47
				4–22	+35	0.29	0.23	0.06	21
				4–23	....	0.29	0.23	0.06	21
				4–24	....	0.19	0.19	None	None
				4–25	....	0.21	0.21	None	None
				4–26	....	0.21	0.21	None	None
				4–27	+38	0.13	0.13	None	None
				4–28	....	0.23	0.22	0.01	4
				4–29	....	0.24	0.24	None	None
				4–30	....	0.24	0.24	None	None
				5–1	....	0.19	0.19	None	None
				5–2†	....	0.17	0.17	None	None
				5–3	....	0.37	0.26	0.11	30
				5–4	....	0.36	0.24	0.12	33
				5–5	....	0.32	0.26	0.06	19
				5–6	....	0.22	0.21	0.01	5
				5–7	....	0.22	0.21	0.01	5
				5–8	....	0.23	0.23	None	None
				5–9	....	0.11	0.11	None	None‡
4 . .	44	M	Exophthalmic goiter (patient severely ill)	5–8*					
				5–9	....	0.51	0.31	0.20	39
				5–10	+103	0.46	0.30	0.16	35
				5–11	....	0.58	0.29	0.29	50
				5–12	....	0.34	0.18	0.16	47
				5–13	....	0.39	0.25	0.14	36
				5–14	....	0.39	0.25	0.14	36
				5–15	+94	0.24	0.17	0.07	29
				5–16	....	0.36	0.33	0.03	8
				5–17	....	0.24	0.24	None	None
				5–18	+91	0.29	0.29	None	None
				5–19	....	0.27	0.26	0.01	4
				5–20	....	0.31	0.31	None	None
				5–22	....	0.33	0.33	None	None
				5–23	....	0.23	0.23	None	None
				5–24	....	0.29	0.29	None	None
				5–25†	....	0.24	0.23	0.01	4
				5–26	....	0.18	0.18	None	None
				5–27	....	0.49	0.32	0.17	35
				5–28	....	0.49	0.28	0.21	43
				5–30	....	0.38	0.30	0.08	21
				5–31	....	0.24	0.24	None	None

* Administration of iodin started.
† Thyroidectomy performed.
‡ Incomplete.

The basal metabolic rate may or may not decline parallel with the decrease in the amount of creatin excreted. Palmer was also unable to establish any constant relation between the metabolic rate and the amount of creatin excreted.

Summary. In a series of 145 cases of hyperthyroidism composed of 115 cases of exophthalmic goiter and 30 cases of adenomatous goiter with hyperthyroidism, creatinuria occurred in 89 cases (61 per cent). The incidence of creatinuria in exophthalmic goiter was 61 per cent and in adenomatous goiter with hyperthyroidism, 63 per cent.

Of 25 female patients with exophthalmic goiter not treated with iodin, creatin was found in the urine of 21 (84 per cent); of 8 men similarly affected and not treated with iodin, creatinuria occurred in all 8.

In a control group of 274 patients not having disease of the thyroid gland, creatin was found in marked or definite amounts in the urine of 14 per cent of the women; in an additional 9 per cent, traces of creatin were found. Creatin in definite or marked amounts was not found in the urine of any of the men; in 9 per cent of the men traces of creatin were found.

Palmer's observation on the effect of the administration of iodin in reducing the amount of creatin excreted by patients with exophthalmic goiter was confirmed. However, the assumption that the reduction of creatinuria is a specific effect of iodin is not justified, as it is equally as logical to assume that the diminished excretion of creatin occurs as a result of the improvement in the general health of patients with exophthalmic goiter which follows the administration of iodin.

For a few days immediately after thyroidectomy the excretion of creatin in exophthalmic goiter may increase in amount or occur when it has been previously absent, even though the administration of iodin is continued.

BIBLIOGRAPHY.

1. Denis, W., and Kramer, J. G.: The Influence of Protein Intake on Creatin Excretion in Children, J. Biol. Chem., 1917, **30**, 189.

2. Denis, W., and Minot, A. S.: The Production of Creatinuria in Normal Adults, J. Biol. Chem., 1917, **31**, 561.

3. Denis, W., and Minot, A. S.: Creatinuria and Acidosis, J. Biol. Chem., 1919, **37**, 245.

4. Palmer, W. W.: The Effect of Iodin on Creatinuria in Hyperthyroidism, Proc. Soc. Exper. Biol. and Med., 1927, **25**, 229.

5. Palmer, W. W., Carson, D. A., and Sloan, L. W.: The Influence of Iodin on the Excretion of Creatin in Exophthalmic Goiter, J. Clin. Inves., 1929, **6**, 297.

6. Shaffer, P. A.: Protein Metabolism in Exophthalmic Goiter, J. Biol. Chem., 1907, **3**, 13.

HEREDITARY AND FAMILIAL DIABETES MELLITUS.

By Irving Sherwood Wright, A.B., M.D.,
INSTRUCTOR IN THE DEPARTMENT OF MEDICINE, NEW YORK.

(From the Department of Medicine, New York Post-Graduate Medical School o Columbia University.)

Heredity has been recognized as an etiologic factor in the causation of diabetes mellitus since the time of Rondelet, of Montpellier, in the early sixteenth century.

Chart I.—Familial and Hereditary Occurrence in Diabetes.

	Year.	Cases studied.	Per cent occurrence.
Schmitz[1]	1874	..	21.1
Frerichs[2]	1884	400	9.75
Flint[3]	1886	..	27.7
Zimmer[4]	1889	..	10.6
Seegen[5]	1893	..	14.0
Grube[6]	1895	..	7.9
Wegeli[7]	1895	..	29.0*
Fitz, Joslin[8]	1898	..	23.8
Bouchard[9]	1899	..	25.0
Kulz[10]	..	692	21.6
Williamson[11]	..	500	22.0
Pleasants[12]	1900	..	5.3
Naunyn[13]	1906	398	17.0
Von Noorden[14]	1917	..	25.4
Hoogslag[15]	1922	..	43.0
Montoro[16]	1924	400	18.0
Seckel[17]	1925	391	26.4
John[18]	1927	1000	9.7
Joslin[19]	1923	2800	21.0
Joslin[19]	1927	2646	25.5
Cammidge[20]	1928	800	28.0

* Children.

Of 21 of the more important statistical reports dealing with this subject 13 give percentages of occurrence of familial and hereditary diabetes as over 21 per cent. John's figures of 9.7 per cent are the lowest we have noted for 30 years.

That the factor of heredity plays an important part as an etiologic consideration in the causation of diabetes in children, is well demonstrated by the experience of Joslin and Marble.[21] In the series of 12 diabetic children who had lived for 10 years or more there was an actual hereditary or familial history in 84.9 per cent. In their 200 living cases the incidence was 31.5 per cent, whereas in their 195 fatal cases the incidence was 21 per cent, essentially the same figure as found by Joslin in his entire series. Joslin recently observed, on the basis of these and other figures, that the longer diabetic children lived the more common hereditary factors became, merely because more time was allowed for others in the family to

develop the disease. Brief mention of some of the instances of familial or hereditary diabetes which have been reported since the time of Rondelet should be made. I have included only families in which 4 or more cases developed. Morton[22] reported 4 diabetic children in a family of 7 in 1696, Isenflamm[23] reported 7 cases in one family in 1784, Storer[24] (1798) reported 4 cases in one family, Fardel[25] 6 cases, Mosler[26] 6 cases, Roberts[27] 8 cases, Pavy[28] 6 cases, Flint[29] 6 cases, Frew[30] 4 cases, Fitz[31] 13 cases (patient had 2 diabetic wives), Neumann[32] 6 cases, Pribram[33] 5 cases and 1 doubtful case, Heiberg[34] 6 cases, Allen and Mitchell[35] 8 cases, Foster[36] 4 cases in one family, 4 cases in another family, Langaker[37] 5 cases, Joslin[38] 14 cases in one family, 8 cases in another family and Kennedy[39] 10 cases. In 1859 Griessinger[40] could only find 3 instances in the literature of familial diabetes.[22,23,24]

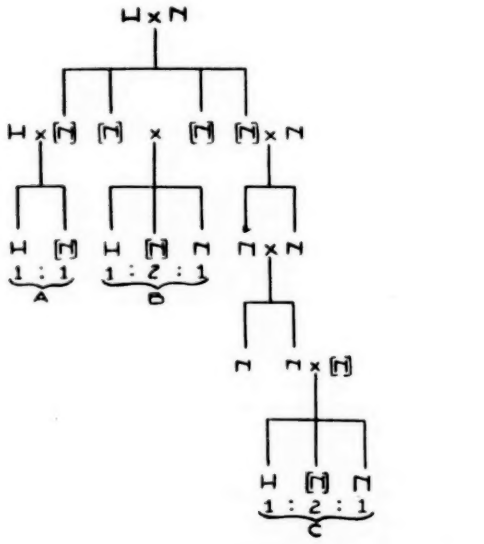

H x N
H x [N] [N] x [N] [N] x N
H [N] H [N] N N x N
1 : 1
A
1 : 2 : 1
B
N N x [N]
H [N] N
1 : 2 : 1
C
H-High Blood Sugar. N-Normal Blood Sugar
[N]-Heterozygous Normal (Hybrid carriers)

CHART II.—Experimental breeding of mice (Cammidge).

Since many cases of diabetes have, no doubt, escaped diagnosis throughout the life span of the patient, and since it is really unusual in the United States for a patient to know any details concerning his ancestors of several generations, or even his slightly distant relatives, complete hereditary charts are difficult to obtain. Physical characteristics have often been shown to follow, in general, the Mendelian law of heredity, but it remained for Howard and Cam-

midge,[41] in England, to demonstrate for the first time experimentally the transmission of a chemical characteristic according to the Mendelian law.

These workers found that if certain mice having a high fasting blood sugar (116 to 120 mg. per cent) were mated they produced offspring having the same high blood sugar, but if mice having these high blood sugars were crossed with mice having normal blood sugars (about 85 mg. per cent) all of the progeny possessed normal blood sugars. One could conclude that in these experiments the high blood sugar played the part of the recessive characteristic. When these seemingly normal offspring were crossed with high blood sugar mice the results followed the Mendelian law, namely, there were equal numbers of high blood sugar mice and seemingly normal mice or hybrid carriers. If the seemingly normal mice (hybrid carriers) were mated with each other the progeny had high and normal blood sugars in the proportion of 1 to 3. This demonstrated that the heterozygous normal or hybrid carriers, although apparently normal were capable of transmitting the characteristic to their offspring with results following the Mendelian law.

Cammidge and Howard further found that if they mated their hybrid carriers with true normals from another stock all of the offspring had normal blood sugars. If these were again mated with true normals the progeny were apparently normals. This could be repeated through many generations with identical results, but if 2 related offspring from such crossings were mated, or if 1 of these mice was mated with another mouse with similar ancestry, some of the progeny would show a high blood sugar in the proportion of 1 to 3. It could then be demonstrated that 2 of the remaining 3 mice were hybrid carriers, and that only 1 was normal and incapable of transmitting the chemical characteristic. This proved how easily a characteristic might be recessive and remain hidden for many generations only to show when the proper mating qualifications were met. If further workers substantiate this work it appears of great significance, since it not only clearly demonstrates the transmission of a certain tendency to a specific blood sugar level, but also suggests that future experiments may determine that other chemical constituents of the blood may follow the law of Mendel.

Cammidge[20] later found similar results while using other animals and also reported a series of cases of diabetes mellitus in English families wherein the same laws were followed. In this latter study he was especially fortunately situated, since we in America find it much more difficult to find families who have adequate knowledge of their ancestry. He found that in the cases where the disease was transmitted as a dominant characteristic the course of the disease was found to be mild, whereas in the cases where the characteristic was recessive the course was usually grave from the onset.

It is my object to present below a series of cases of interest from the viewpoint of hereditary and familial diabetes mellitus. Most of these patients were seen in the Metabolic Clinic of the New York Post-Graduate Hospital. Several were seen in private practice.

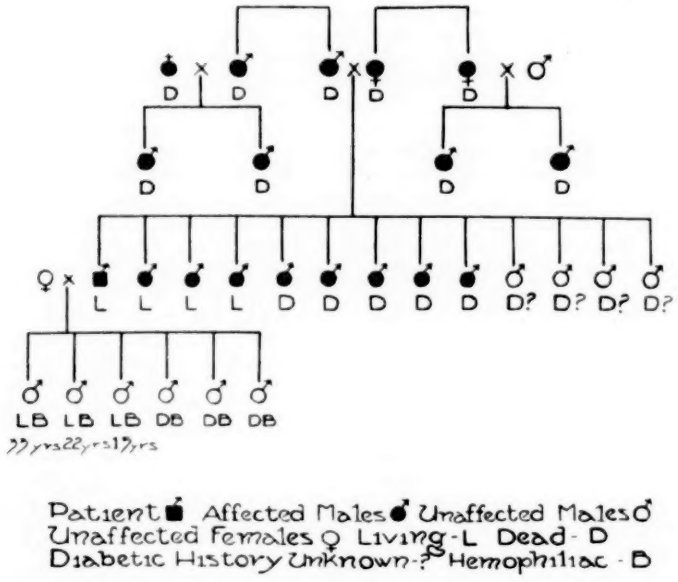

D D D D D
D D D D
♀ x L L L L D D D D D D? D? D? D?
LB LB LB DB DB DB
Patient Affected Males Unaffected Males
Unaffected Females ♀ Living-L Dead-D
Diabetic History Unknown-? Hemophiliac-B

CHART III.—Hereditary and familial chart of patient J. F.

NOTE.—Dominance of diabetes mellitus. Dominance of male offspring. Although patient's offspring have thus far failed to develop diabetes, they have all been bleeders, 2 having died from hemorrhage after tonsillectomy.

Case Reports. CASE 1.—J. F. The accompanying hereditary chart shows an unusual dominance of the disease, but the results are what one should anticipate following the mating of two diabetics, especially if the disease was a dominant characteristic in them. The patient, aged 59 years, was a Hebrew. His occupation was that of a candy machine salesman. He used alcohol to excess. There was no serologic evidence of syphilis. At the time he was first seen in the Metabolic Clinic of the Post-Graduate Hospital, October 24, 1929, he had diabetes mellitus of 18 years' duration. He was also suffering from an atrophic polyarthritis of 3 years' duration and early cardiac failure of 6 months' duration. During the first 16 years of his illness he had taken large doses of alkalis (50 to 100 gm. of various kinds a day). During the past 2 years he had tried insulin twice but had frequently hypoglycemic reactions, so discontinued its use. Two months preceding admission he fell from a wagon, lacerating his scalp. This wound became infected, which brought him to the hospital. Three years before admission he weighed 195 pounds, although he was only 5 feet 5 inches tall (marked obesity). Six months before admission he weighed 165 pounds and at the time of admission 120 pounds.

Physical Examination. Positive findings on admission:

Head—infection infiltrating soft tissues over most of frontal region. *Pupils*—react sluggishly to light; left pupil larger than right. *Tonsils*—large and obviously infected. *Gums*—edentulous except for a few old roots; marked pyorrhea. *Neck*—small, shotty cervical lymph nodes, also felt in left inguinal and right epitrochlear regions. *Chest*—emphysematous in type with usual accompanying signs. *Heart*—sounds of poor quality; rhythm irregular with frequent premature beats; rate average, 85; moderate enlargement to the left in the third, fourth and fifth interspaces, A2 greater than P2; no murmurs heard. *Abdomen*—normal; liver at costal margin. *Reflexes*—all deep reflexes markedly diminished; knee jerks and Achilles reflexes could not be elicited. No pathologic reflexes were noted. *Fundi*—high hyperopia; both eyes showed soft exudates at the macula.

Course in Hospital. On admission a casual specimen of urine showed 9.5 per cent sugar. He was placed on a diet containing carbohydrate, 60 gm., protein, 45 gm., fat, 105 gm. (total calories, 1407) (Mosenthal Diabetic Diet No. 3), and was given insulin, 40 units, daily, in divided doses. He became sugar-free quickly and the insulin was reduced to 20 units in five days and discontinued in 15 days, because the patient was then having frequent hypoglycemic reactions. The infection had meanwhile cleared up. Five days after admission his heart suddenly gave evidence of failure, the liver border showing 3 fingerbreadths below the costal margin. Digitalization by moderate dosage was begun. Three days later Cheyne-Stokes breathing was noted while the patient was asleep, which ceased when he was awakened. After a thorough neurologic examination Dr. Sherwood concluded that there was no evidence of intracranial pathology; that the reflex changes were due to a diabetic polyneuritis. The following day the heart became regular and the patient was discharged in 3 weeks, November 25, 1929, on a dosage of tincture of digitalis, 20 minims t.i.d., and a diet of carbohydrate, 80 gm., protein, 60 gm., fat, 140 gm. (total calories, 1876) (Mosenthal Diabetic Diet No. 4). No insulin was then required. A summary of his laboratory findings accompanies.

LABORATORY FINDINGS, BLOOD CHEMISTRY.

Date.	Sugar, mg. per cent.	Cholesterol.	Uric acid.	Urea.	Creatinin.	CO_2 combining power.
Oct. 14, 1929 . .	0.256	0.169	...	31.2	...	43.8
Oct. 25, 1929 . .	0.089	0.188	4.0	25.0	2.3	47.5
Nov. 1, 1929 . .	0.163	0.200	...	22.0	...	
Nov. 4, 1929 . .	0.150	...	...	...	...	42.8
Nov. 11, 1929 . .	0.096					
Nov. 22, 1929 . .	0.275	...	...	...	...	62.6
Dec. 20, 1929 . .	0.120	0.204	...	...	...	53.2
Mar. 12, 1930 . .	0.138	0.152	...	18.3	...	46.6
Mar. 21, 1930 . .	0.286	...	4.4	18.3	...	45.0
Mar. 25, 1930 . .	0.109	...	...	23.2	...	47.5

NOTE.—There seems to be no relationship between the blood sugar and cholesterol levels.

December 5, 1929. The patient suddenly developed a complete right homonymous hemianopsia. This cleared up gradually and completely by December 19, 1929. At the latter date the patient was readmitted, having gained from 133 to 162 pounds in 14 days with the development of marked edema and ascites. On December 5, 1929, he was on the above-mentioned

diabetic No. 4 diet and showed 4.2 per cent sugar in a 24-hour specimen of urine. A curious phenomenon then took place. As his edema increased he violated his diet, eating all kinds of carbohydrate foods and even taking sugar on his food and in his coffee. In spite of that intake of carbohydrate with the increase in edema the urinary sugar dropped to negative as measured by the Benedict qualitative test, the fasting blood sugar being as low as 0.12 per cent. This took place without the use of insulin. He was discharged in good condition in 1 week and returned, March 12, 1930, again decompensated. Once more he was discharged in good condition and has not returned for further treatment.

Spinal Fluid. Wassermann, 0. Colloidal-gold curve, 11232100000. Cell count, 1 lymphocyte. Butyric acid test, 1+.

Blood Wassermann Test. Negative.

Blood Count. Slight secondary anemia otherwise normal throughout.

Urine. Specific gravity varied from 1.029 to 1.011. Reaction, acid throughout. Sugar, 9.4 to 0 per cent. Diacetic acid and acetone were absent throughout. Albumin absent during the first admission; 1+ during all later admissions.

The blood pressure varied from 122 systolic and 70 diastolic to 92 systolic and 60 diastolic.

Discussion. Certain points are of great interest and importance in the above history. The outstanding feature is the unquestionable transmission of the tendency toward the development of diabetes as a dominant characteristic. The history was attested by both the patient and his wife. The 4 brothers who died of a questionable condition died in Russia during the World War. We can conclude that the patient's diabetes was mild in character for 18 years and he stated that his relatives all had the disease for many years before dying. This is in accordance with Cammidge's statements in reference to instances where the disease is transmitted as the dominant characteristic. Another curious fact is that, although the patient's children have not as yet developed diabetes, they have been, without exception, bleeders (hemophiliacs), as diagnosed by physicians, and that 2 of them have died as a direct result of hemorrhage following tonsillectomy.

The neurologic findings have also been of interest. The finding of pseudotabes of diabetes, as determined by the absent or reduced knee jerks and Achilles tendon reflexes, was recognized simultaneously by Borchardt[42] and Althaus[43] in 1884. Since that time many studies have been made to determine the location of the lesion and the mechanism which produces it. Sandmeyer,[44] Naunyn[45] and Leyden and Goldscheider[46] believed that the process represented the combined sclerosis of pernicious anemia first described by Lichtheim.[47] Williamson, in a series of studies,[48] and Schweiger[49] concluded that the changes in the posterior column were secondary to degeneration in the intramedullary portion of the posterior roots; in other words, essentially, the same as in tabes dorsalis. Kraus[50] concluded that clinical evidence was in favor of a lesion proximal to the juncture of the roots. Charcot[51] felt that most diabetic disorders of this type must be due to peripheral neuritis. Woltman

and Wilder,[52] in a recent careful study of changes in the spinal cord and peripheral nerves of diabetics, found the spinal cord changes to be relatively unimportant as compared to the changes in the peripheral nerves. The location of the significant nervous lesions in these cases probably varies in different cases and hence no universal agreement can be reached.

The mechanism causing these changes is likewise undetermined. Grube[53] claimed to have observed marked neuritis after subcutaneous or intravenous injection of dextrose into rabbits but his work has not been confirmed. Auché[54] applied sugar locally and by injection to the sciatic nerves of guinea pigs and concluded that sugar was not the cause of degeneration. Eichhorst[55] kept the nerves of man and frog in solutions of dextrose, acetone and oxybutyric acid for several days with no effect.

The possibility of infection, so common in diabetics, as the etiologic factor was suggested by Patrick.[56] In the 10 cases reported by Woltman and Wilder[52] in which neuritic changes were marked the acetone and sugar were under careful control. It seems logical in agreement with these authors to feel that if sugar or acetone bodies were responsible for such changes they would be found more frequently in young, severe diabetics rather than in chronic mild cases. They are actually much more common in the latter group.

The sudden occurrence of the right homonymous hemianopsia with its subsequent rather rapid clearing up would incline us to think of this happening as a cerebral accident; either a minute hemorrhage or, more likely, a temporary anemia due to an arteriolar spasm—the area affected was probably in the left cortical visual area or the left visual tract central to the chiasm.

The third very interesting feature was the sudden increased tolerance for sugar with the onset of edema as noted above. That it was not due to a retention in the blood was shown by the low blood-sugar reading. At least three possibilities present themselves by way of explanation: (*a*) This patient had a past history of periods of seeming improvement. He then suffered from hypoglycemic reactions if he was taking insulin, although the dosage and diet might be unchanged. A similar phenomenon may have occurred coincidental with the onset of edema. (*b*) The carbohydrate tolerance may suddenly have been increased due to some other factor. (*c*) There may have been a retention of sugar in the tissues with the fluid. This is unlikely.

Case 2.—E. P. The chart accompanying this history again presents the results of the mating of 2 known diabetics. Four of the 5 offspring have developed the disease and the fifth is still alive and may develop it.

The patient was a Jewess, aged 54 years. The past history, aside from diabetes and the usual diseases of childhood, was essentially negative. The blood Wassermann was negative. The disease had been discovered 10 years previously, when following a period of marked polydipsia the urine

was found to contain sugar. At that time the patient was obese, weighing 198 pounds. On examination she weighed 161 pounds. She had always been of a very nervous temperament. Her chief symptoms were: Weakness, 2 weeks' duration; polyuria, usually about 3½ quarts in 24 hours, 10 years' duration; polydipsia, more than 2 quarts a day; nocturia, once a night; polyphagia, moderate; furunculosis, subsiding on upper lip (on vulvæ 6 years previously).

The positive findings on *physical examination* were as follows: Unusual number of pigmented moles scattered over body; eyes, scleræ cloudy; fundi show marked tortuosity and sclerosis of arteries. Peripheral arteries, sclerotic. Blood pressure was 172 systolic and 90 diastolic to 160 systolic and 90 diastolic. Heart sounds of poor quality; area of precordial dullness enlarged. Apex, 12.5 cm. to the left of the midsternal line in the sixth interspace. The right border was 2 cm. to the right of the midsternal line. Lungs and abdomen negative. The knee jerks were absent.

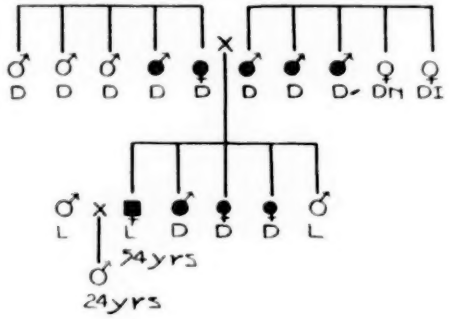


CHART IV.—Hereditary and familial chart of patient E. P. (Case 2.)

Laboratory Findings:

Blood chemistry.	February 24, 1930	May 19, 1930
Urea nitrogen	31.2	15.1
Creatinin	1.4	
Sugar	0.334	0.309
Cholesterol	0.254	

The urine was examined every 2 weeks for many months. The average findings were as follows: Specific gravity, 1.015 to 1.025; reaction, acid; sugar, faint trace to 1.43 per cent; albumin, 1+; acetone and diacetic acid, rarely 1+. The diabetes could be controlled by means of a qualitative diabetic diet, but the patient would not coöperate even to the extent of observing such a simple diet.

Discussion. As will be noted from the chart, diabetes mellitus was present in the families of both of the patient's parents' families in addition to being present in themselves. It would, therefore, be anticipated that a large proportion of the children would be likely to develop the disease if they lived long enough. As in the first case, the diabetes was mild in degree, having been present for 10

years with practically no treatment and no complications. The deep reflexes showed beginning changes as evidenced by the absence of knee jerks. The only child of the patient is only 24 years of age, and since the patient married an apparent normal it is impossible to predict whether that child will develop the disease or not.

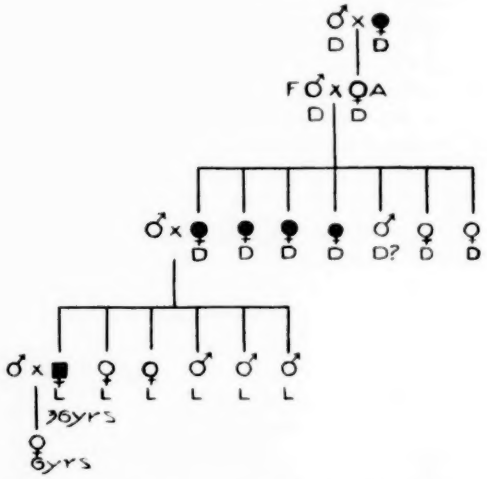


CHART V.—Hereditary and familial chart of patient H. B. (Case 3.)

CASE 3.—H. B. First seen, January 15, 1930. The accompanying chart illustrates an instance in which the disease was transmitted through the female members of the family and in which it skipped a generation to reappear in 4 members of the next generation. If we accept the law of Mendel in this family tree figure A and F must have been a hybrid, capable of transmitting the disease, even though not afflicted with it. Even then the number of diabetic offspring is unusual.

The patient was of English descent, aged 39 years. She was married and had 1 child, 4 years of age. The past history was negative except for frequent attacks of tonsillitis, "scarlatina" in childhood and influenza in 1918. She had always been fond of sweets.

Her complaints were: Painful areas throughout the body and nervousness. She had lost 6 pounds in the past few months. Her appetite was very good and bowels were regular. The physical examination revealed nothing abnormal except a slight lateral scoliosis. The blood pressure was 130 systolic and 170 diastolic.

Laboratory Findings. Blood Chemistry. Sugar, 0.375 mg. per cent. Uric acid, 4. Urea nitrogen, 10. Creatinin, 1.

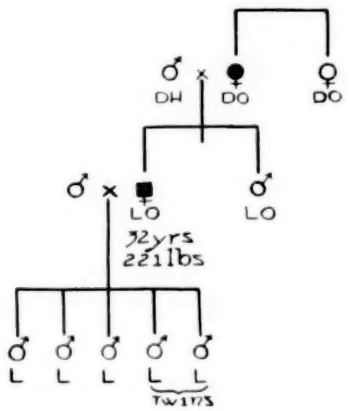
Urine. Specific gravity, 1.016 to 1.035. Sugar, 6.66 per cent to 0; negative throughout for acetone and diacetic acid tests.

Wassermann Test. Negative.

Blood Count. Red blood cell, 5,312,000; white blood cell, 6500; hemoglobin, 80 per cent; polymorphonuclears, 71 per cent; small lymphocytes, 25 per cent; large mononuclear cells, 4 per cent.

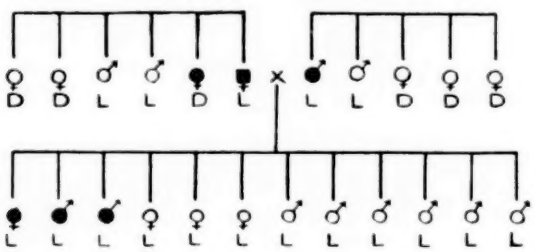
This patient improved quickly on a qualitative diabetic diet.

The remaining charts illustrate a number of instances in which there have been 3 or more cases of diabetes mellitus in an immediate family, except Chart VI, in which family obesity was very common.



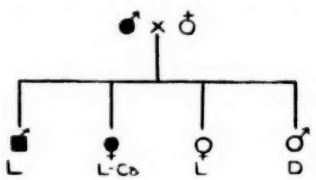
Code as in Chart III Obesity-O Heart disease-H
Note prevalence of Obesity in this family

CHART VI.—Hereditary and familial chart of patient B. LaG.



Code as in Chart III

CHART VII.—Hereditary and familial chart of patient M. C.



Code as in Chart III Cancer of the Breast-Ca

CHART VIII.—Hereditary and familial chart of patient A. B.

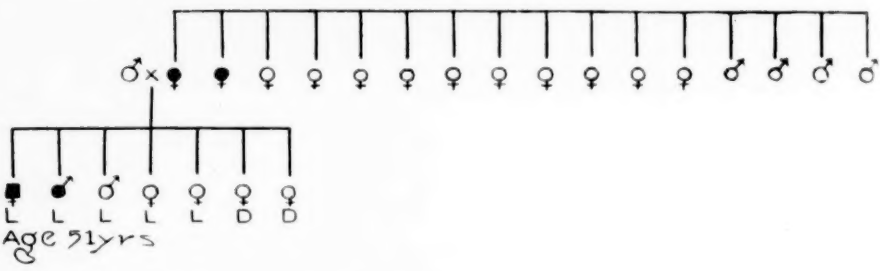


CHART IX.—Hereditary and familial chart of patient C. S.

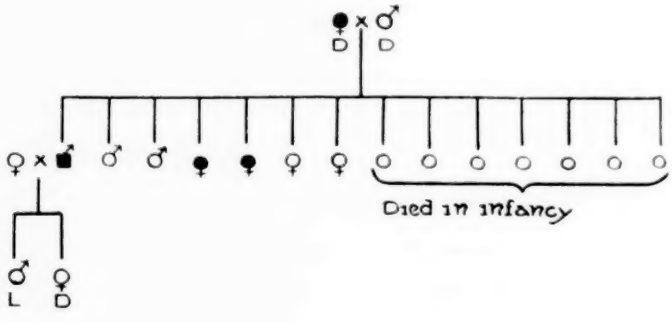


CHART X.—Hereditary and familial chart of patient S. S.

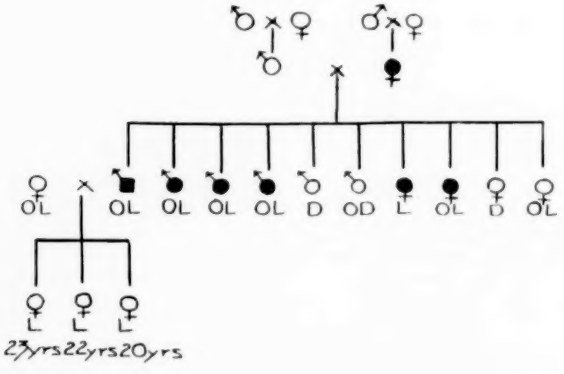


CHART XI.—Hereditary and familial diabetes mellitus, patient Z. K.

Discussion. It has not been my purpose to prove that all cases of diabetes mellitus are inherited or familial. It is, however, increasingly evident that these factors play a more important etiologic part than has hitherto been generally recognized. It is also possible that identical living conditions and dietary habits such as those resulting in obesity may be causative factors in producing more than 1 case of diabetes in a family. There are also many mild diabetics who are, no doubt, missed and hence omitted from the family trees as such.

There appear to be, then, two groups of factors which tend to produce diabetes mellitus in an individual. Hereditary tendency, H or h, and acquired factors, AF or af (infections, obesity, etc.). Diabetes mellitus is in many cases the product of the two factors. The same result is obtained whether the hereditary factor is large and the acquired factor is small or *vice versa*, hence:

$$H \times af = D$$

or

$$h \times AF = D$$

Needless to say, if the two groups of factors are both large the disease would theoretically be inevitable, while if they are both present but small, or if one is absent, the patient may never manifest evidence of the disease during life. Individuals in the last group are often discovered when blood-sugar determinations are made in the healthy members of a diabetic patient's family. Such a formula in its present form must not be used as an index of severity of the disease, but only as an index as to tendency to develop diabetes, *i. e.*,

$$H \times AF = D$$

might not develop into a severe case as other factors which we cannot evaluate at present must be introduced. A similar suggestion was made by Loeb[57] some years ago in reference to the etiology of cancer. Our cases have been in agreement with Cammidge's contention that when the characteristic was dominant the disease tended to be mild.

Summary. A tendency to high blood sugar can be transmitted according to the law of Mendel in mice and other animals. It is suggested that the disease diabetes mellitus can be transmitted according to the same laws in human beings. All cases of diabetes are probably not hereditary, but careful questioning will increase the incidence of this occurrence in the records of a series of cases. Certain cases are presented to illustrate and emphasize the hereditary and familial factor of diabetes in the human race.

BIBLIOGRAPHY.

1. Schmitz: Klin. Wchnschr., 1874, p. 555.
2. Frerichs: Ueber den Diabetes, Berlin, 1884, p. 185.
3. Flint: J. Am. Med. Assn., 1886, **6**, 427.
4. Zimmer: Schnée, Diabetes, London, 1889, p. 59.

5. Seegen: Der Diabetes Mellitus, Berlin, 1893, p. 123
6. Grube: Ztschr. f. klin. Med., 1895, **27**, 468.
7. Wegeli: Arch. f. Kinderh., 1895, p. 57.
8. Fitz and Joslin: J. Am. Med. Assn., 1898, **31**, 165.
9. Bouchard: Traité de médécine, Paris, 1899.
10. Kulz, quoted by Joslin: See Reference 19.
11. Williamson, quoted by Joslin: See Reference 19.
12. Pleasants, J. H.: Bull. Johns Hopkins Hosp., 1900, **11**, 325.
13. Naunyn, quoted by Joslin: See Reference 19.
14. Von Noorden, quoted by Joslin: See Reference 19.
15. Hoogslag, quoted: J. Am. Med. Assn., 1922, **2**, 1934.
16. Montoro: Diabetes y su Tratamiento Actual, Habana, 1924, p. 20.
17. Seckel: Ztschr. f. klin. Med., 1925, **102**, 195.
18. John: Arch. Int. Med., 1927, **39**, 67.
19. Joslin, E.: Treatment of Diabetes Mellitus (monograph), 4th ed., 1928, p. 143.
20. Cammidge: Diabetes Mellitus and Heredity, Brit. Med. J., 1928, **2**, 738.
21. Joslin and Marble: See Reference 19, p. 822.
22. Morton, R.: Opera medica, Amsterdam, 1696, **1**–**8**, 22–24.
23. Isenflamm: Versuch einiger praktischen Anmerkungen über die Eingeweide, Erlangen, 1784.
24. Storer: Rollo's Cases of Diabetes Mellitus, 1798.
25. Fardel, D.: Traité clinique et therapeutique due diabéte, Paris, 1869, p. 296.
26. Mosler: Brit. Med. J., 1864, **8**, 734.
27. Roberts: Urinary and Renal Diseases, London, 1885, p. 245.
28. Pavy: Deutsch. med. Wchnschr., 1885, **12**, 478.
29. Flint: J. Am. Med. Assn., 1886, **6**, 420.
30. Frew: Glasgow Med. J., 1887, **27**, 272.
31. Fitz: Diabetes Mellitus, Oxford Medicine, Oxford University Press, 1921, **4**, 131.
32. Neumann: Familiarer Diabetes, Deutsch. med. Wchnschr., 1916, **42**, 1053.
33. Pribram, H.: Ueber die Vererbung der diabetischen Konstitution, Zentralbl. f. inn. Med., 1915, **36**, 328.
34. Hieberg, K. A.: Bemer Kungen zum erblicken Diabetes, Deutsch. med. Wchnschr., 1916, **42**, 255.
35. Allen, F. M., and Mitchell, J. W.: A Case of Hereditary Diabetes, Arch. Int. Med., 1920, **25**, 648.
36. Foster, N. B.: Consanguineal Diabetes Mellitus, Bull. Johns Hopkins Hosp., 1912, **23**, 54.
37. Lanaker: Deutsch. med. Wchnschr., 1911, **37**, 217.
38. Joslin: See Reference 19.
39. Kennedy, S.: Hereditary Diabetes Mellitus, J. Am. Med. Assn., 1931, **96**, 241.
40. Griessinger: Studien über Diabetes, Arch. f. physiol., Heilk., 1859, **3**, 16.
41. Howard and Cammidge: J. Genetics, 1926, **16**, 3, 387.
42. Borchardt, H.: Ueber die Veränderungen de Aterienmedia bei Spontangangrän und ihre Beziehung zum Diabetes, Virchow's Arch. f. path. Anat., 1926, **259**, 521.
43. Althaus, J.: On Sclerosis of the Spinal Cord, Including Locomotor Ataxia, Spastic Spinal Paralysis and Other System Diseases of the Spinal Cord: Their Pathology, Symptoms, Diagnosis and Treatment, London, Longmans, Green & Co., 1885, p. 278.
44. Sandmeyer, W.: Beitrag zu pathologischen Anatomie des Diabetes Mellitus, Deutsch. Arch. f. klin. Med., 1892, **50**, 381.
45. Naunyn, B.: Der Diabetes Mellitus, in Nothnagel's Specielle Pathologie und Therapie, Vienna, Hölder, 1900, **7**, 251.
46. Leyden and Goldscheider: Die Erkrankungen des Rückenmark und der Medulla oblongata, in Nothnagel's Specielle Pathologie und Therapie, Vienna, Hölder, 1900, **10**, 500.
47. Lichtheim, quoted by Sandmeyer: See Reference 44.
48. Williamson, R. T.: Changes in the Posterior Column of the Spinal Cord in Diabetes Mellitus, Brit. Med. J., 1894, **1**, 398; Changes in the Spinal Cord in Diabetes Mellitus, Ibid., 1904, p. 122; On the Knee Jerks in Diabetes Mellitus, Lancet, 1897, **2**, 138; Diabetic "Neuritis," Practitioner, 1924, **112**, 85; The Symptoms Due to Peripheral Neuritis or Spinal Lesions in Diabetes Mellitus, Rev. Neurol. and Psychiat., 1907, **5**, 550; Note on the Tendo-Achilles Jerk and Other Reflexes in Diabetes Mellitus, Ibid., 1903, **1**, 667; Diseases of the Spinal Cord, London, Henry Frowde, Hodder and Stoughton, 1908, p. 371.

49. Schweiger, L.: Ueber die Tabiformen Veränderungen der Hinterstränge bei Diabetes, Wien. med. Wchnschr., 1907, **57**, 1549.

50. Kraus, W. M.: The Clinical Involvement of the Peripheral Nerves in Diabetes Mellitus, J. Nerv. and Ment. Dis., 1920, **52**, 331; Involvement of the Peripheral Neurons in Diabetes, Arch. Neurol. and Psychiat., 1922, **7**, 202.

51. Charcot, J. M.: Sur un cas de paraplégie diabétique, Arch. de neurol., 1890, **19**, 305.

52. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus, Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med., 1929, **44**, 576.

53. Grube, K.: Ueber das Verhalten der Patellarreflexe bei Diabetes Mellitus, Neurol. Cntralbl., 1893, **12**, 770; Gastrische Krisen bei Diabetes Mellitus nebst Bemerkungen über die Behandlung der Verdauungsstörungen der Diabetiker, München. med. Wchnschr., 1895, **42**, 136; Ueber das Verhalten des Blutzuckers in Fällen von diabetischer Neuritis und Neuralgie, Deutsch. Ztschr. f. Nervenh., 1918, **60**, 302.

54. Auché, B.: Des altérations des nerfs périphériques chez les diabétiques, Arch. d. méd. exper. et d'anat. path., 1890, **2**, 635.

55. Eichhorst, H.: Neuritis diabetica und ihre Beziehungen zum fehlenden Patellarschnenreflex, Arch. f. path. Anat., 1892, **127**, 1.

56. Patrick, H. T., in discussion on Krauss, W. M.: See Reference 50, second article.

57. Wells, H. G.: Ann. Int. Med., 1931, **4**, 678.

INTERPRETATION OF FLARIMETER TESTS.

By L. F. MacKenzie, M.D., P. V. Wells, D.Sc.,

ASSOCIATE MEDICAL DIRECTOR,

BIOPHYSICIST,

AND

E. G. Dewis, M.D.,

ASSISTANT MEDICAL DIRECTOR,

L. S. Ylvisaker, M.D.,

ASSISTANT MEDICAL DIRECTOR,

NEWARK, N. J.

(From the Medical Department of The Prudential Insurance Company of America.)

The physiology of flarimeter tests of circulatory fitness has been presented briefly by the authors in previous papers,[1] but many of those interested have not found it easy to apply these principles to the test in detail. The instrument that we have called the flarimeter has a large orifice for measuring vital capacity, and a small one for determining the degree, if any, of shortness of breath. The blows through each are made at a constant pressure of 20 mm. of mercury, by means of a sensitive water manometer. The ability of the heart and its coördinating mechanisms to adjust themselves to the strain imposed by the increased intrathoracic pressure and changes in the blood is estimated both by the length of blow through the small orifice and by the degree and rate of rise of blood pressure during the blow. We are studying these relationships in an effort

to add to or clarify, if possible, our knowledge of the causes of and variations in them (length of blow and blood pressure) and their significance. While wishing to avoid announcing premature opinions, the following general considerations must be thoroughly understood before attempting to interpret any flarimeter tests. Our own clinical experience to date is about 100 cases, while from selected field examiners we have received reports on 1044 adult males and 132 females, so that with those by unselected examiners, and those made at the Home Office, our experience covers well over 1500 cases. A brief analysis of this experience is presented.

Empirical Normal Borderlines. The nearest we can get to a typical test on a healthy adult male is to take the median* value for each response. Only "first-class" risks, those without present or previous record of impairment were chosen, about 70 per cent of those given insurance at standard rates. Moreover, the only cases used were those from a small group of specially selected examiners, to exclude (as far as possible) errors of observation and technique. Home Office tests were also excluded to keep the series homogeneous. The results are shown in Fig. 1. Unfortunately, circumstances prevented using the standard exercise in many cases, in others the standard steps were used but not the standard number of ascents by age and weight, so that only 174 were given truly standard exercise. The final blow, 2 minutes after exercise, was so recently introduced that Tr refers to only 131 cases.

Under "Remarks" in Fig. 1 are shown the values tentatively adopted as "Normal," and the borderlines between "Normal" and "Abnormal." These do not refer to a particular blow but to the best of the three trials in each case. Thus, the median value of Tm is that of the longest blows in Test III taken from each report, and so must be longer than the medians for each blow. The longest T_{20} of the three is similarly taken, but the value of S_+ is not necessarily the longest, as it must refer to the same blow as that from which Tm is taken. Round numbers are adopted as normal, and they are purposely made slightly severe because it is expected that performance will improve somewhat in the future.

The abnormal borderlines are so chosen that about 5 per cent of healthy adult males should fail to pass each border. This condition is met in vital capacity and in $(Tm-S_+)$, one of the measures of irritability, but the borderlines for shortness of breath appear to be too severe. The factor of personal performance, however, must not be forgotten, particularly in Te and Tr, the lengths of the blows after exercise in Test V, which result from single trials only. The effect of these borderlines for Tm and $(Tm-S_+)$, the best measures at present of shortness of breath and irritability, is compared with those of the diastolic pressure (at rest) in Table 1, on 500 cases in

* One-half the values are on each side of the median, by definition.

FIG. 1.—MEDIAN VALUES FOR 470 "FIRST-CLASS" ADULT MALES.
(By 70 selected examiners.)

I.		II.			III.				IV.		V.	
At rest.		Vital capacity.			Blows with small orifice (Blow 3, 388 cases).				At rest.		Standard exercise, small orifice blow (174 cases).	
		Seconds	Liters.		1.	2.	3.					
Pulse rate	76	1.	21	4 2					Rate	76	Pulse rate before	76
Systolic	120	2.	21	4 2	Systolic	120	123	124	Systolic	122	No. of ascents	22
Diastolic	76	3.	21	4 2	T_{20} seconds	35	35	38	Diastolic	78	No. of bendings	
					Maximum systolic	151	155	158			Length of blow, seconds	19
					Total seconds	47	50	52			Pulse rate, end of 2 minutes	74
This line for Home Office use only		Per cent of normal		108	S_+	31	32	34			Length of blow, seconds	49

Remarks:

Symbol.	Median.	Normal (adopted).	Abnormal below (adopted).	Cases with abnormal response.	Definition.
					Vital capacity.
V	108%	107%	90%	6%	Per cent of normal by height (table of Myers).
					Irritability.
T_{20}	38 sec.	40 sec.	25 sec.	9%	Time for systolic to rise 20 mm.
$Tm-S_+$	20 sec.	20 sec.	0	5%	S_+ = Total systolic rise.
					= Maximum systolic—systolic before blow.
					Shortness of breath.
Tm	54 sec.	55 sec.	40 sec.	8%	Length of blow before exercise.
Te	19 sec.	20 sec.	15 sec.	10%	Length of blow 10 seconds after exercise.
Tr	49 sec.	50 sec.	40 sec.	11%	Length of blow 2 minutes after exercise.

the first three columns, and (in the last column) on those in the first 1000 cases from which all impaired cases were excluded except those having nothing abnormal but arterial tension.

TABLE 1.—RELATIVE FREQUENCY OF ABNORMAL ARTERIAL TENSION, IRRITABILITY AND SHORTNESS OF BREATH—ADULT MALES.

	First 500 cases not rated for occupation.			Without impairment except arterial tension.
	Standard.	Rated.	Rejected.	
Number of cases	298	94	108	738
	Percentage of above numbers of cases with this impairment.			
Impairment.	Per cent.	Per cent.	Per cent.	Per cent.
Hypertension { Diastolic 100 or over	1	3	22	2
Hypertension { Diastolic 90 or over)	15	20	38	12
Hypotension (diastolic under 60)	1	2	6	3
Irritability ($Tm-S_+$ negative)	6	4	18	5
Shortness of breath (Tm under 40)	9	15	30	8

Evidently shortness of breath as defined by failure to blow 40 seconds is more frequently encountered than cardiac irritability, as indicated by a rise in systolic pressure numerically greater than the length of the blow. Among insurable cases both irritability and shortness of breath are more frequent than abnormal diastolic pressure. Does this mean a poor choice of borderline, or is it of clinical significance? Not necessarily, because a short Tm by itself may not always indicate shortness of breath, for the three measures Tm, Te and Tr must check to be consistent. If they do not, the simplest explanation is poor performance in the short blows. Similarly, $(Tm-S_+)$ and T_{20} should check. We must, therefore, class as consistently normal or abnormal only those cases in which the responses check, while reports with a single response abnormal must be considered as inconsistent. Such inconsistencies are inherent in all tests depending upon personal performance. To discount properly the factors of performance and emotion is an essential preliminary to the interpretation of flarimeter reports.

Analysis of Responses. A further study of the tests on first-class risks is presented in Table 2. Two-thirds (65 per cent) of the reports are consistently normal, that is, all the responses are above the abnormal borderlines, while nearly one-third; (29 per cent) are inconsistent. Most of the inconsistencies are in the "nonstandard" tests, and when they are further analyzed it is seen that 13.8 per cent, or nearly half the inconsistencies are in Te. As most of the tests are "nonstandard" because the exercise given was thirty bending movements in 1 minute, evidently this produces more breathlessness than does the standard step exercise, although the return to normal is the same, for Tr fails in 1.7 per cent of each type of test.

TABLE 2.—ANALYSIS OF RESPONSES IN FLARIMETER TESTS.

(By 70 selected examiners on 470 first-class male risks.)

Type of test.	Standard.	Non-standard.	Total.
Number of cases	174	296	470
	Per cent.	Per cent.	Per cent.
Percentage of above numbers of cases giving:			
1. Normal tests	78	58	65
2. Consistently abnormal tests	7	5	6
3. Inconsistent tests, total	15	37	29
(*a*) Single response abnormal	13	26	21
(*b*) Evidently inconsistent	..	5	3
(*c*) Perfunctory performance	2	6	5

	Responses consistently abnormal.			Inconsistent single response Ab (3a).			Inconsistent (3b).	Inconsistent (3c).
Type of test.	Standard.	Non-standard.	Total.	Standard.	Non-standard.	Total.	Non-standard.	
Number of cases	174	296	470	174	296	470	296	
Per cent of cases with this response abnormal (in number of cases on line below).								
Number of cases	12	16	28	174	296	470	16	19
Subnormal.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Rate (Test IV)	25	12	18	0	0	0	6	5
Systolic (Test IV)	0	0	0	0	0	0	6	0
Diastolic (Test IV)	0	0	0	0	0	0	0	0
V	17	31	25	4.6	1.4	2.6	12	37
T_{20}	0	88	50	0.6	6.4	4.3	31	5
$Tm-S_+$	33	62	50	1.7	1.0	1.3	12	11
Tm	33	62	50	0	1.0	0.6	31	58
Te	58	62	61	4.6	13.8	10.4	69	89
Tr	100	50	93	1.7	1.7	1.7	31	

There are too many failures (4.6 per cent) in Te, even among the standard tests, but nevertheless we do not feel that 15 seconds is too severe a borderline, because considerable improvement in performance is to be expected. Moreover, shortness of breath should first appear immediately after exercise (Te), later 2 minutes after (Tr) and finally, when well established, even before exercise (Tm). With the borderlines adopted the failures do increase in the expected order. Among the eight standard tests (4.6 per cent) showing nothing abnormal but vital capacity, 6 showed underweight; in fact, the average underweight was 4 pounds, the average vital capacity 16 per cent below normal. This means body-build, as will be explained later.

The group "consistently abnormal" includes all cases in which two or more responses failed to rise above the borderlines, but which were not evidently inconsistent. The cases in this group were therefore short of breath, showed irritability, or the two combined. Twenty-eight (6 per cent) of first-class risks fall in this group, so that the odds are about 15 to 1 that a healthy adult male will not give a consistently abnormal report. Of course, some of the "first-class" risks may not be really first-class (without present or previous

impairment), and a closer study might reveal an impairment which has been overlooked but is indicated by the flarimeter test. The fact that, on the average, three or four responses are abnormal in each case lends color to this suspicion.

The large percentage (29) of inconsistent reports is to be expected. All the difficulties and possible failures of 70 beginners, most of whom never saw the technique demonstrated, are included. But errors of performance and technique are not the sole cause of inconsistent reports as undoubtedly some seeming inconsistencies now are not yet understood.

The values to be studied first in a flarimeter test are the pulse rates and blood pressures at rest (Tests I and IV). Table 1 suggests that there is no systematic change in normal cases, but a more detailed study shows that the pulse pressure usually increases when the diastolic falls, and *vice versa*, and these usual coördinations indicate no great change in the work of the heart but merely passing emotion. The diastolic is higher in Test IV in about one-third of the tests, and in these the pulse pressure is usually lower. When the changes are small it seems reasonable to assume that this indicates a return to rest from a more active state in Test I, but an excessive rise in diastolic, combined with a distinct fall in pulse pressure, suggests vasoconstriction coming to the relief of a fatiguing heart muscle with possibly impaired intracranial circulation. The large and small orifice blows of Tests II and III, however, should not fatigue the heart, and recovery should be complete by Test IV. Our results show that the normal range of emotional variation (up or down) can be taken as about 20 mm. systolic, 10 mm. diastolic, and 15 pulse beats per minute. These borderlines agree with the clinical experience of Stieglitz,[2] who suggests that emotional hypertension is likely to become permanent and lead to degenerative circulatory changes.

Now there are five values of the systolic at rest, including the baseline of Test III, and two of the diastolic. If all show hypertension, we must assume its presence. The same system of checking is applied to all flarimeter responses. Satisfactory interpretation is dependent on a religious observance of the time schedule. By comparing the responses in this way with a standard performance, each serves as a control on the others, and an estimate of circulatory fitness is obtained that must ultimately prove superior to present methods.

An analysis of over 1000 reports on adult males is shown in Table 3. Flarimeter reports were disregarded in the Company's action on the cases in this table. Cardiac impairments, blood pressure, urinary findings, toxic goiter and overweight were the only impairments included. First and second class under company action must not be confused with first and second class under flarimeter report. Standard risks have been subdivided into two

classes, "first-class," those without present or previous impairment, "second-class," those with impairments too minor to rate. "Normal" reports are those in which every response is above its abnormal borderline; these are subdivided into two classes, "first-class," those above the median in all responses, "second-class," the remaining normals.

TABLE 3.—COMPARISON OF FLARIMETER REPORTS WITH COMPANY ACTION.

(All adult male risks except those rated for occupation, by 70 selected examiners.)

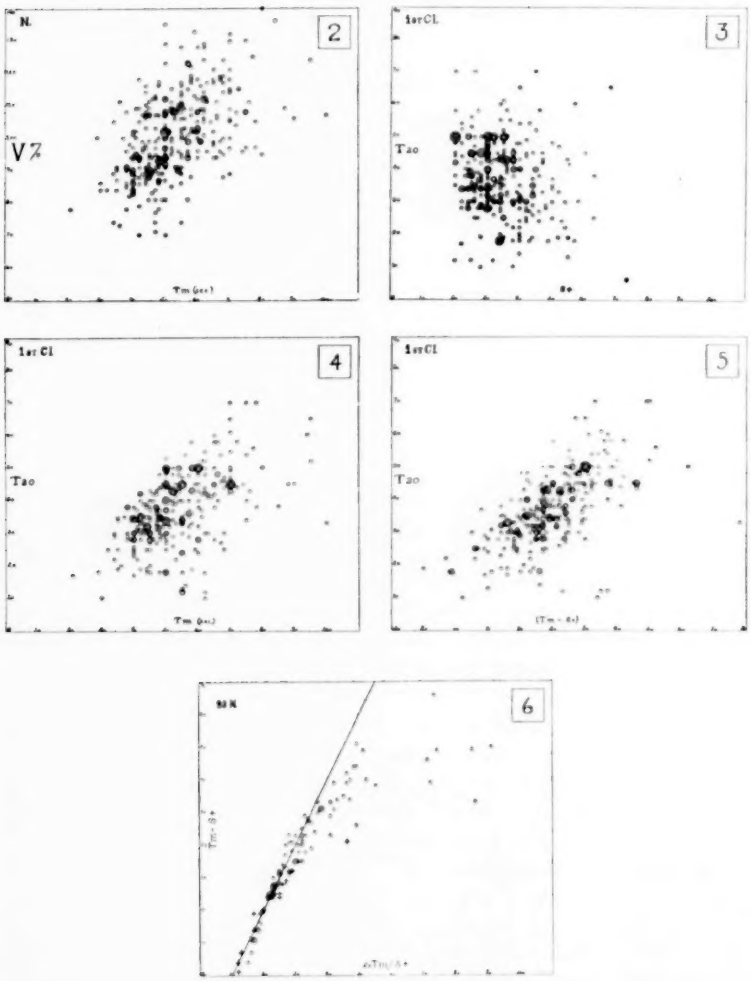
		Type of flarimeter report.							
		First-class.		Second-class.		Consistently abnormal.		Inconsistent.	
Company action.	Total cases.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
1. First-class	490	86	18	218	44	29	6	157	32
2. Second-class	207	36	17	105	51	12	6	54	26
3. Rated	179	20	11	63	35	27	15	69	39
4. Rejected	168	6	4	43	26	72	43	47	28
Total	1044	148	14	429	41	140	13	327	31

The statistics indicate clearly that a normal flarimeter report is characteristic of a standard risk, for the frequency of second-class risks is maximum (51 per cent) for second-class reports. Only 6 per cent of first-class risks give consistently abnormal reports, which checks Table 2. Among the rejected risks it will be noted that but 4 per cent pass first-class tests, while 43 per cent give consistently abnormal reports. Thus, in spite of the large number of inconsistent responses, which include beginners' errors, perfunctory performance and types not yet numerous enough to classify, there can no longer be reasonable doubt that the flarimeter gives a real test of circulatory fitness.

The data on females are too few to define normals, as yet, but the first 132 give frequencies quite like Table 3 when the borderlines and medians for each response are taken as 5 points below those for males. Children show still shorter blows and a marked emotional instability, in the few cases studied.

Correlation of Responses. As reports began to accumulate in number, the empirical relations between the responses were reconnoitered by scatter diagrams. Over 40 of these were made on Home Office normals, first-class, standard, rated and rejected risks from the field, both male and female, for different pairs of responses. They showed positive correlation between V and Tm among the rated and rejected risks, and for all groups between Tm and T_{20}, while a negative correlation was shown between T_{20} and S_+. None of the groups showed any correlation between V and T_{20}, V and S_+, or between Tm and S_+, although a positive correlation would be expected in the latter case, and undoubtedly would be found in successive tests upon a single subject, because the longer one blows the higher the systolic rises.

This early experience with the test indicated no correlation between vital capacity and length of small orifice blow among Home Office normals and standard risks, in agreement with Jackson



CORRELATION OF RESPONSES

Charts 3, 4 and 5 show that T_{20} is more closely related to $(Tm-S_4)$ than to either (Tm or S_4). Chart 6 shows that $(Tm-S_4)$ is proportional to $(20\ Tm/S_4)$ near the abnormal borderline.

and Lees, but further data from selected examiners in the field gives a positive correlation of 49 per cent, as shown in Table 4 and Chart 2. This could reasonably be expected, but it may also indicate

that some doctors were more successful than others with both V and Tm. If such is the case the suggestion of a necessary physiological relation between V and Tm must be taken with reserve. The effect of exercise upon them is utterly different, for vital capacity is not reduced at all, while Te, the length of small orifice blow begun 10 seconds after exercise, is less than half Tm, the length before exercise, showing that it is much better than vital capacity as a measure of shortness of breath.

TABLE 4.—CORRELATION COEFFICIENTS OF 309 FIRST-CLASS MALES.

Variables.	Correlation 100r per cent.	Prediction $(100\ 1-\sqrt{1-r^2})$, per cent.
Maximum length of blow:		
Before exercise (Tm, sec.) and 10 sec. after exercise (Te, sec.)	51	14
Vital capacity (per cent V) and Tm	49	13
Tm and T_{20}	42	9
V and Te	32	5
T20 and $(Tm-S_+)$, 453 cases	60	20

The failure of S_+ to correlate with Tm when T_{20} did, was puzzling at first, for both T_{20} and S_+ were believed to be measures of the tolerance of the circulation to increasing acidity. As the difference was thought to be that T_{20} was standardized while S_+ was not, a rough correction for the length of blow was introduced by taking the difference $(Tm-S_+)$. This simple measure of irritability was found to be more closely related to T_{20} than was Tm, as a glance at Charts 4 and 5 will show. Now probability theory would suggest less correlation between T_{20} and $(Tm-S_+)$ than between T_{20} and Tm, because there is practically no correlation of T_{20} with S_+, and combining these two quantities at random would be expected to vitiate the correlation. But Table 4 shows that by taking the function $(Tm-S_+)$ instead of S_+, we have increased the correlation from 42 to 60 per cent. This is almost as high as the correlation between height and weight, so that we are justified in regarding both T_{20} and $(Tm-S_+)$ as measures of irritability, and using one as a check on the other.

To compare these two measures of irritability quantitatively, they must be expressed in the same units. This can be done by taking the differences $(T_{20}-20)$ and $(Tm-S_+)$, but neither represents any geometric quantity on the systolic response curve. T_{20} is the slope in arbitrary units of the line from the origin to the point representing a 20-mm. rise in systolic, so that the smaller T_{20} the more rapid the systolic rise to this point. The ratio $(20\ Tm/S_+)$ expresses in the same units the rapidity of the total systolic rise during the blow, and should normally be less than T_{20}. If both are equal the origin and the points $(T_{20}, 20)$ and (Tm, S_+) are all three in line.

The ratio (20 Tm/S_+) is too involved for ordinary use. The borderline is fortunately $Tm = S_+$, and then the ratio reduces to 20. The borderline for T_{20} however, is 25, which again expresses the fact that the systolic pressure rises more rapidly after T_{20} has been reached. The scatter diagram (Chart 6) shows the relation of $Tm–S_+$ to (20 Tm/S_+), the circles representing first-class risks, the crosses clinical cases. The straight line ($20\ Tm/S_+ = 20 + (Tm–S_+)/2$) shows that the approximation is good enough for practical purposes near the abnormal borderline, in other words, that the difference is in direct proportion to the ratio, so that in practice it is sufficient to glance at S_+ and see how it compares with Tm. If numerically greater it indicates irritability, and to check, T_{20} should be less than 25 seconds.

The number of cases in Table 4 is such that the probable error is about 3 per cent. It must be remembered that the coefficient of correlation expresses the percentage of the variations in the two responses which can be considered related, but the percentage of the variations in one response which can be predicted from those in the other is much smaller, as shown in the last column of the table. The coefficient ($r = 0.51$) for example, proves that 51 per cent of the variations in Tm are proportional to those in Te, but only the fraction ($1–\sqrt{1–R^2}$) or 14 per cent can be predicted. To be able to predict even 50 per cent, the correlation would have to be at least 87 per cent, because of the confusion introduced by the random components of the variation. Thus, if weight is 70 per cent correlated with height among normals, only 30 per cent of the variations in weight can be predicted from height.

TABLE 5.—CORRELATION OF BLOOD PRESSURE RESPONSES.
(Adult males, unimpaired or abnormal in arterial tension only.)

Variables.	No. cases.	Correlation, 100r, Per cent.	Prediction, $100(1-\sqrt{1-r^2})$, Per cent.
Systolic (S) and:			
Diastolic (D), all values	738	69	28
Diastolic D 80 and over	335	68	27
Diastolic D under 80	403	40	8
Pulse pressure (S–D) and:			
Diastolic (D), all values	736	−15	1
Diastolic D 80 and over	332	26	3
Diastolic D under 80	404	−13	1
Irritability ($Tm–S_+$) and:			
Diastolic (D), all values	738	− 8	0
Diastolic D 80 and over	335	−18	2
Diastolic D under 80	403	1	0
Pulse pressure (S–D), all values	736	−10	0
Shortness of breath (Tm), all values	738	58	19
Shortness of breath (D 90 and over)	85	47	12
Shortness of breath (D 60 to 89)	634	56	17
Shortness of breath (D under 60)	19	63	22

A more systematic study of the correlation of blood pressure responses is presented in Table 5. The high correlation of systolic

and diastolic pressure is, of course, familiar, but the coefficient is not, and so is computed as a basis for comparison. Apparently, the pulse pressure tends to rise above normal in both hyper- and hypotension, although the correlations are small. Irritability tends to increase slightly, that is $(Tm-S_+)$ to decrease, when the diastolic departs from normal, and also when the pulse pressure increases, but irritability accompanies shortness of breath much more frequently. The steady increase in this correlation from 47 ± 6 per cent among the high diastolics, through 56 ± 2 per cent for the normals, to 63 ± 9 per cent among the low diastolics is suggestive, but the probable errors are too large to ascribe significance to this apparent trend.

The Analysis of Overweight. The Medico-Actuarial Investigation[3] showed a very wide spread among standard risks of the same sex, age and height, about the average weight for each class, which indicates that two individuals of the same sex, age and height may differ markedly in build and yet be normal. Therefore, the deviation from average weight may be partly due to a factor not necessarily related to impairment, and if this factor is properly corrected for, it is reasonable to expect a closer correlation with mortality than can be obtained from height and weight alone.

Vital capacity appears to be the most practicable anthropometric constant to use as a correction factor for body-build. It is more accurate than chest expansion or than the chest-waist difference. Moreover, in itself it is an important physiologic constant, for it indicates the alveolar surface available for oxygen exchange. Its reduction, therefore, must be considered an impairment, although the safety factor is large, and moderate limitation in vital capacity does not in itself lead to shortness of breath.

Now vital capacity is about as closely correlated with height as weight is, so it is reasonable to expect individuals with vital capacities above normal for a given height to be somewhat overweight because of build alone, and not because of excess fat. In other words, weight should normally increase with vital capacity at constant height, and such positive correlation would not indicate impairment. Overweight as an impairment should be negatively correlated with vital capacity.

Mortality is found to increase also among underweights at the younger ages. Vital capacity should, therefore, be below normal among impaired underweights, that is, it should be positively correlated with weight. For example, in pulmonary tuberculosis the weight and vital capacity go down together as the disease advances.

The measure of shortness of breath (Tm), however, would not be expected to vary in the same way as a function of weight, for it is practically independent of height. A combination of overweight with reduced Tm and V, therefore, is cumulative evidence of impairment on three counts at once, while moderate overweight with

normal Tm and large V indicates merely an individual of large build. Hence, such a class of overweights may be regarded as less impaired than others with the same excess weight.

Our data are as yet to meager to test these ideas with any conclusiveness, but a preliminary study of 700 cases already shows that the general direction of the results is just as expected except for standard underweights. Only 14 cases were rated for overweight alone; 3 of these showed both irritability and shortness of breath, 1 shortness of breath, 2 borderline shortness of breath, and 8 gave normal flarimeter reports. All showed vital capacity normal or above. The percentage of abnormal reports is nearly twice, and that of inconsistent about one-third the average percentage for all rated cases. Thus, the test may prove quite useful in estimating the burden of overweight.

The only correction that has been made in vital capacity is to add 1 per cent per year over age 40 to the percentage of normal from Myers' tables by sex and height, "but this correction is evidently too much. One-half per cent per year over 40 would probably be nearer the average decrease with age."[4]

Progressive Stages of Impairment. It is already fairly evident that most of the responses in flarimeter tests increase with increase in function, and that reduction spells impairment. No one can believe that additional lung capacity (V) is any handicap, and the lengths of blow (Tm, Te, and Tr) before and after exercise cannot decrease very much before one is conscious of shortness of breath. The irritability indexes (T_{20} and $Tm - S_+$), also show no tendency to increase, but always to decrease as impairment proceeds, at least in typical heart cases, until the disease is advanced. The older measures, pulse rate and blood pressure, on the other hand, present optimum values above and below which the interpretation is less favorable.

The borderlines between normal and abnormal, too, are approximately established. It will take a long time, however, for the precise meaning of the flarimeter report to be known, for the possible varieties are innumerable. Suppose each response were limited to two values, "good" or "bad." Even then there would be over 33 million different reports possible, by permuting the 25 different responses on each report. Eleven of these, however, may be regarded as checks, leaving 14 which are significantly different. These 14 would still furnish over 16,000 varieties of reports. But each response can have many more than two values, indeed, it is only a point on a continuous quantitative scale. Failure to appreciate these complexities is perhaps responsible for the shallow enthusiasm and impatient skepticism sometimes accorded such tests.

The most casual inspection of flarimeter reports, however, is sufficient to show that the responses are not random. They possess a close relationship which reduces enormously the varieties encoun-

tered. Apparently the first sign of circulatory trouble is the irritability shown by a shortened T_{20} and an exaggerated systolic rise (S_+ larger than Tm). It is not certain which of these signs is the more sensitive, probably they represent much the same thing. Sometimes this is preceded or accompanied by emotional hypertension.

The next stage is shortness of breath, which should appear first as a reduction in Te, then in Tr, and finally in Tm, although differences in performance may easily confuse the issue. Irritability should be more marked at this stage, but the vital capacity should be normal.

As the cardiac impairment advances, even the vital capacity begins to be reduced, and finally the heart muscle fails to produce sufficient systolic response. Advanced cases, however, perform so poorly that one never feels sure that a short blow with insufficient systolic response represents any approach to an individual's possible limit.

Most of the heart cases fall into place in this scheme which appears rational on physiologic grounds. There are not enough cases yet, however, to justify systematic presentation. The most consistently abnormal tests were met in hypertension (57 per cent of 37 rejected cases), particularly when complicating a heart murmur (63 per cent of 16 cases). On the other hand, only 5 per cent of 19 cases called "functional murmur" by the examiner, but nevertheless rated, gave consistently abnormal flarimeter reports, while normal reports were obtained in 48 per cent of 21 cases rejected with heart murmurs as against 12 per cent of 16 cases with both murmurs and hypertension.

Apparently, murmurs, hypertrophy, abnormal pulse or blood pressure, toxic goiter, tuberculosis and overweight are the impairments with which the typical picture we have outlined is most consistent. Cases with glycosuria or albuminuria, however, seem to present quite a different type of flarimeter test. Thus, in 43 cases rated or rejected for sugar or albumin in the urine, only 21 per cent of 14 glycosurias showed irritability and only 3 per cent of 29 albuminurias; 21 per cent of the former showed consistent shortness of breath, 14 per cent of the latter. Only one each showed both irritability and shortness of breath, 3 and 7 per cent, respectively. The outstanding characteristic seemed to be a very marked reduction in Tr relative to Tm. We suspect that such cases may often show responses different from the cardiac type, perhaps due to changes in the acid-base balance of the blood and tissues.

We do not yet begin to know the functional pathology of the respiratory center, the tolerance of which to acidity largely determines the length of blow. In some conditions, such as uncomplicated chronic pulmonary emphysema, an exaggerated tolerance to CO_2 is developed,[5] but in uncomplicated cardiac impairments, appar-

ently, the burden is borne by the myocardium, and a tolerance to acidity does not develop or may even be reduced. Thus, we cannot interpret fully, as yet, an insufficient systolic response with no shortness of breath, which we have encountered a few times, apparently, in both normal and abnormal cases.

Errors of Performance. If no steps are available the exercise is not standard, that is, the amount of work done is neither measurable nor under control. Nevertheless, we are not utterly helpless, for Te, the length of blow immediately after exercise can be used as a gauge of the oxygen debt incurred. If this is normal (about 20 seconds), the exercise may be considered approximately standard, although it is evident that substandard exercise may produce the normal Te in a substandard case. Moreover, a subnormal Te may indicate merely that the bending movements were made with more than standard vigor. Such doubts do not occur with the standard step exercise, in which the rate and amount of work done are accurately controlled, so that for comparative purposes and doubtful cases the exercise test should always be standard.

The examiner must not allow excessive overbreathing either before or between small orifice blows, for this washes carbon dioxid out of the blood and enables the subject to blow longer. A certain amount of overbreathing, of course, is to be expected. It is the conscious effort to increase his score that must be guarded against, or taken into consideration in the interpretation.

There is one other trick which may slip by unperceived, while the examiner is absorbed in following the systolic rise. This is "breath-snatching." Whenever attempted, the water in the manometer falls abruptly, as indeed does the systolic pressure, so that it is immediately evident, and the test should be stopped and begun again. It is rarely attempted if the doctor stresses the necessity of holding the manometer level steady.

The usual error of performance, however, is the failure of the individual to give a blow approaching his physiologic limit. In such cases the systolic pressure often fails to rise even 20 mm., and such tests are of little value. Without real coöperation no functional test requiring conscious effort can possibly succeed. Fortunately, most subjects enjoy the test and do their best. Others, who mean well but are unfamiliar with the subjective sensations of air hunger, can be encouraged to put forth a real effort. Their second and third blows in Tests II and III are usually quite successful.

When the doctor himself makes the test, the allowances to be made for errors of performance are fairly obvious at the time of the test, and should be recorded immediately in the space for remarks, as a part of the original data. But suppose one attempts to interpret a test made by another, the values recorded are often

the only data available. To illustrate how we would handle Test III, the series of responses shown in Table 6 are interpreted as single blows, although in an actual case all the evidence must be considered.

TABLE 6.—INTERPRETATION OF TEST III.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
Systolic	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
T_{20} (sec.)	40	35	20	20	40	30	25	30	40	20	20	29	30	..	15
Maximum systolic	150	160	160	180	180	150	160	160	160	145	160	145	140	130	160
T_{20} (sec.)	60	50	50	50	50	40	40	35	35	35	30	30	30	25	25
S_+ (mm.)	30	40	40	60	60	30	40	40	40	25	40	25	20	10	40
Classification:															
Tm	N	N	N	N	N	B	B	A	A	A	A	A	A	A	A
Tm–S_+	N	N	N	A	A	N	B	A	A	N	A	N	N	N	A
T_{20}	N	N	A	A	N	N	N	N	N	A	A	A	N	..	A

N = normal; B = borderline; A = abnormal.

Interpretation.

(1) Exceptionally good (examiner may have missed maximum systolic).
(2) Perfectly normal (probably correct).
(3) Probably normal (T_{20} may be an error).
(4) Consistently irritable (probably correct).
(5) Blew his best, but slightly under par (T_{20} looks a bit too long).
(6) Not his best, no abnormality shown.
(7) Irritable and short of breath.
(8) A suspicious test, repeat (may have missed T_{20}).
(9) Irritable and short of breath (T_{20} a mistake).
(10) Irritable and short of breath perhaps (probably missed peak in systolic).
(11) Consistently irritable and short of breath.
(12) Probably irritable and short of breath (missed systolic peak or else T_{20}).
(13) Consistent perfunctory performance (values check).
(14) Either lazy or advanced case of myocardial degeneration.
(15) Advanced irritability and shortness of breath (toxic goiter?).

The data in Test V are compared in the same spirit, trying to visualize the performance at each step and giving the subject the benefit of the doubt wherever possible, for one good response is usually more significant than two bad ones. Indeed, if we assume correct observations, we must be liberal with the systolic responses, for emotional disturbance may easily cause momentary fluctuations which cannot be taken too seriously. When irritability appears in more than three out of the six systolic responses in Test III, however, it cannot be considered lightly, especially if the Tm's, Te and Tr are not consistently good. If all three Tm's are bad, both Te and Tr should also be bad, of course, but if three of the five are good, the other two may be due to faulty performance. Every effort of persuasion should be made to get the longest possible final blow (Tr). It is a great advantage to have the systolic responses during this blow also, as we do in our latest technique, for this often settles the question. When Tr is a bit short, a normal T'_{20} and $(Tr-S'_+)$

are reassuring, especially when Test III is normal, and when Tr is exceptionally long, these values help in revising our estimate of Test III. On the other hand, if Te is poor, and the pulse and blood pressure returns delayed, and both T'_{20} and $(Tr-S'_{+})$ are short, a subnormal Tr cannot reasonably be assumed to be merely an accident, as some patients will claim.

W. W. Herrick[6] considers that the most satisfactory exercise test for all types of cases is the performance of enough work to bring about moderate dyspnea. For ambulatory patients, however, the better standardized exercise of Master and Oppenheimer which we have adopted is quite practical, and the length of flarimeter blow immediately thereafter measures quantitatively the dyspnea produced. It is, therefore, much more satisfactory for comparative purposes.

In Fig. 1, Test V shows three responses to exercise: (1) Shortening of the blow immediately after; (2) extent of return of pulse toward its original rate, at the end of the second minute; (3) length of blow 2 minutes after exercise (allowing for the interruption in breathing during the previous blow). As now standardized, however, a further improvement in the test has been made by leaving the cuff and stethoscope attached to the arm (disconnecting the tubes) during the standard step exercise and then observing the pulse, systolic and diastolic returns and the systolic response during the final blow. This increases the number of observations to *eight*, without taking any more time, and so provides a very complete picture of the response to exercise. Further details will be gladly supplied to those interested.

Summary. Normal values and abnormal borderlines for all flarimeter responses are determined empirically.

By analysis of the first 1500 cases, a basis is established for interpretation.

Individuals with vital capacities above normal for a given height should appear somewhat overweight because of build alone. Vital capacity is the best available factor for correcting overweight by height, age and sex.

Cardiac impairments seem to show the following progressive changes:

1. *Irritability, i. e.*, shortened T_{20} and exaggerated systolic rise; often accompanied by emotional hypertension.

2. *Shortness of breath*, the length of flarimeter blow, first reduced 10 seconds after standard exercise, then 2 minutes after also, and finally both before and after exercise. Irritability should be more marked at this stage, but the vital capacity should be normal.

3. Further shortness of breath, but less irritability.

4. Even the vital capacity reduced.

5. Insufficient systolic response.

Atypical flarimeter tests, showing CO_2 tolerance, but great shortening of breath after exercise, seem to characterize the 43 uncomplicated urinary cases so far accumulated. Complicated cardiorenal cases give too great a variety to classify the few tests as yet available.

REFERENCES.

1. Proceedings of Fortieth Annual Meeting, Assn. Life Ins. Med. Dir. America, 1929, **16**, 36; Am J. Med. Sci., 1930, **180**, 372.
2. Stieglitz, E. J.: Am. J. Med. Sci., 1930, **179**, 775.
3. Medico-Actuarial Mortality Investigation, vol. **1**, Assn. Life Ins. Med. Dir. and Actural Soc. of America, New York, 1912.
4. Report to Assn. Life Ins. Med. Dir., 1930, vol. **17** (in press).
5. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, 6th ed., 1930, p. 627.
6. Herrick, W. W.: Ann. Int. Med., 1929, **3**, 467.

THE EFFECT OF BLOOD TRANSFUSIONS ON BONE-MARROW ACTIVITY AS INDICATED BY THE RETICULOCYTE COUNT.

By Carl Reich, A.B., M.D.,

ASSISTANT BACTERIOLOGIST AND SEROLOGIST, LENOX HILL HOSPITAL, NEW YORK CITY.

(From the Achelis Laboratory, Lenox Hill Hospital, New York.)

The use of blood transfusions as a therapeutic agent is finding an ever-widening field in practically all branches of medicine. It is, therefore, of considerable interest to determine how transfusions act and what effect they have on the blood-forming organs. It is obvious that the immediate benefit derived from a transfusion is the result of the purely mechanical addition of a certain volume of blood to the circulation. Many transfusions are given for this reason alone, as in cases of hemorrhage. However, it is also a common practice in hospitals to transfuse patients who are depleted by disease, but who have not actually had any direct loss of blood. Transfusions in cases of this character are usually small in amount, but frequently repeated. Clinicians speak of these as stimulating transfusions, and the inference is that they not only have an immediate effect in supplying blood, but also have a subsequent stimulating action on the hematopoietic system. The purpose of this work is to study the effect of a number of unselected routine transfusions on the bone marrow. The percentage of reticulocytes in the peripheral blood is used to estimate bone-marrow activity.

Hess[1] and Itami,[2] who were the first to describe the changes in

the bone marrow after transfusion, used the histologic changes in the bone marrow of rabbits as criteria of the effect of the transfusions. Their results were not conclusive, since there is considerable normal variation in the red marrow of normal rabbits.

Robertson,[3] and subsequently Krumbhaar and Chanutin,[4] studied the effects of experimental plethora on the bone marrow of rabbits and dogs, using the percentage of reticulocytes as an index of bone-marrow activity. There was no notable change in the percentage of reticulocytes until the animals had been given several transfusions. When the plethora became well defined the number of reticulocytes in the blood began to diminish.

Vogel and McCurdy[5] studied the reticulocytes in cases of pernicious anemia after transfusion. They found, in several cases where large amounts of blood had been given, a marked drop in the reticulocytes. These patients did badly. Minot and Lee[6] observed a similar effect after large transfusions in pernicious anemia. This severe depression and poor clinical result has been explained as follows: In severe cases of pernicious anemia the marrow is very nearly exhausted. The stimulus of the anemia with its oxygen lack is just enough to keep it functioning. A sudden lowering of this stimulus is produced by a large transfusion and the activity of the marrow is markedly depressed. It follows, therefore, that in cases of pernicious anemia with feebly reacting bone marrow, as indicated by the reticulocyte count, small transfusions are preferable to large ones.

Our series consists of 25 cases and 6 controls. These cases vary in the diseased condition present and in the amounts of blood transfused. They have been studied with particular reference to the reticulocyte response after transfusion. We would disclaim all responsibility for the amounts of blood transfused, since these amounts were specifically ordered by the clinicians.

Technique. Blood counts, including reticulocyte percentage, were done before transfusing the patient and at varying intervals afterward for 2 weeks. This time limit was considered sufficient for any marked changes to occur. Similar counts were done on the donors so as to check up on the number of reticulocytes in the transfused blood. The counts were done in the usual way (hemoglobin by the Sahli method, red counts with carefully standardized pipettes, and reticulocytes on cover-slip preparations stained with brilliant cresyl blue (Grübler) and counterstained by the Jenner-Giemsa method). In estimating the percentage of reticulocytes 1000 red cells were counted, using an oil-immersion objective with a special grating ocular. The donors had red blood counts averaging from 4,000,000 to 5,000,000, with reticulocytes between 0.5 and 1 per cent. The transfusions were done by the Lindemann multiple syringe method.

Case Reports.

	Hb., per cent.	R.B.C. millions per c.mm.	Retic., per cent.	Transfusion, cc.	Diagnosis and remarks.
Case 1:					
May 19	25	0.75	7.0		Pernicious anemia
May 20	...	...	...	600	
May 21	32	0.8	3.9		Liver treatment
May 23	35	2.0	4.0		
May 25	40	2.0	4.5		Female, aged 39 years
May 28	45	2.2	4.8		
May 29	...	...	...	400	
May 30	59	2.9	3.9		
May 31	...	...	...	600	
June 2	70	3.9	2.0		
June 3	...	...	...	600	
June 4	80	4.0	0.6		
June 5	...	...	...	500	
June 6	90	4.4	0.4		
Case 2:					
April 10	41	2.1	2.0		Anemia primary(?)
April 11	...	...	...	300	
April 12	48	2.6	1.6		Female, aged 51 years
April 14	45	2.4	1.5		
April 16	49	2.5	1.6		
April 20	50	2.8	1.3		
April 22	53	2.9	1.7		
April 25	55	3.1	1.5		
Case 3:					
April 8	59	4.0	4.0		Multiple myeloma
April 9	...	...	...	250	
April 10	65	4.2	2.0		Male, aged 25 years
April 12	63	4.0	2.0		
April 15	60	3.8	2.5		Patient left hospital
April 19	57	3.6	3.0		
April 25	50	3.2	4.0		
April 26	...	...	...	250	
April 27	54	3.0	3.3		
April 29	50	2.8	3.5		
May 1	...	...	...	250	
May 2	64	3.1	1.8		
Case 4:					
October 29	43	2.6	1.6	300	Bleeding gastric ulcer
October 30	50	3.2	2.0		
November 3	62	3.5	2.0		Male, aged 35 years
November 6	56	3.0	1.0		
November 12	62	3.8	0.4		
Case 5:					
April 17	70	4.1	0.6	300	Uterine fibromyomata
April 18	78	4.5	0.5		
April 19	...	...	...	250	Female, aged 31 years
April 20	84	5.0	0.2		
April 23	85	4.6	0.4		Hysterectomy
April 27	83	4.3	0.7		
May 1	85	4.5	0.5		

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Transfusion, cc.	Diagnosis and remarks.
Case 6:					
May 17	60	3.1	2.1	200	Acute mastoiditis
May 19	68	3.9	2.6		
May 21	70	4.1	2.0		Female, aged 4 years
May 22	...	...	...	200	
May 23	77	4.9	2.2		Operation
May 27	75	4.4	1.8		
May 30	75	4.3	1.6		
Case 7:					
October 9	35	1.8	11.0	350	Primary anemia
October 10	45	2.1	9.5		
October 13	60	2.2	5.0		Female, aged 63 years
October 14	...	...	...	350	
October 15	61	2.3	1.0		Liver treatment
October 17	54	2.4	0.4		
October 19	55	2.2	0.1		
October 23	59	2.7	0.1		
Case 8:					
October 11	53	3.2	0.8	100	Pneumonia
October 13	66	4.2	0.8		
October 15	60	4.0	1.1		Male, aged 10 months
October 17	65	4.3	0.8		
October 20	70	4.5	0.2		
October 24	72	4.4	0.4		
Case 9:					
October 18	65	3.5	0.8	80	Pneumonia
October 20	74	4.0	1.2		
October 22	72	4.2	0.6		Male, aged 6 months
October 24	76	4.3	0.8		
October 28	78	4.5	0.8		
November 1	75	4.2	0.6		
Case 10:					
October 22	65	3.8	0.2	180	Pneumonia
October 23	66	3.9	0.4		
October 25	65	4.0	0.8		Male, aged 2 years
October 27	66	4.1	0.5		
November 1	62	3.2	1.5		
November 6	63	3.4	1.2		
Case 11:					
April 20	63	3.7	2.0		Tuberculosis of kidney
April 21	...	...	...	300	
April 22	65	3.8	2.5		Female, aged 23 years
April 23	...	...	...	300	
April 24	66	4.3	2.0		Nephrectomy
April 28	65	4.0	1.8		
May 1	65	4.2	2.0		
May 5	67	4.1	2.5		
May 14	67	4.3	2.1		
Case 12:					
October 31	28	1.4	0.6	350	Acute myeloblastic leukemia
November 1	45	2.0	0.2		
November 3	35	1.8	0.1		Male, aged 13 years
November 7	25	1.2	0.1		Died; autopsy, diagnosis confirmed

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Transfusion, cc.	Diagnosis and remarks.
Case 13:					
October 29	45	2.3	0.8	400	Carcinoma of lung
October 30	52	2.8	1.0		
November 3	48	2.7	0.6		Male, aged 58 years
November 6	48	3.1	0.8		
November 11	49	2.8	0.8		
November 13	48	3.2	0.8		
Case 14:					
November 4	65	3.6	0.2	500	Tuberculosis of ovaries
November 5	68	4.1	0.2		
November 7	63	3.2	0.4		Female, aged 28 years
November 11	65	3.5	0.8		
November 15	63	3.6	0.6		Operation
November 19	56	3.0	0.4		
Case 15:					
November 7	65	3.7	0.9	350	Sepsis(?)
November 10	69	3.9	0.8	350	Male, aged 38 years
November 11	77	4.3	0.1		Died; autopsy, miliary tuberculosis
Case 16:					
November 4	74	6.0	0.8	150	Malnutrition; marasmus dehydration
November 5	110	7.2	1.0		
November 7	105	8.2	0.2		Male, aged 9 months
November 8	...	...	...	150	
November 10	120	9.6	0.2		Died
Case 17:					
December 5	74	4.7	1.0	400	Thrombophlebitis of leg
December 8	63	3.9	1.0		
December 10	69	4.0	0.4		Male, aged 50 years
December 11	68	3.7	0.4		
December 15	69	4.2	1.0		
December 17	70	3.9	0.6		
December 19	70	3.8	1.0		
Case 18					
December 5	46	3.9	0.8	150	Acute mastoiditis
December 8	62	4.5	0.6		
December 10	59	4.3	0.6		Male, aged 1½ years
December 12	63	4.6	0.8		
December 16	67	4.8	0.6		Operation
December 18	65	4.4	0.8		
December 20	67	4.5	0.4		
Case 19:					
December 5	71	4.3	2.0	80	Furunculosis, malnutrition
December 8	93	6.2	1.6		
December 10	74	4.2	0.8		
December 12	70	4.3	0.4		Male, aged 4 months
December 16	75	4.5	0.2		
December 18	72	4.4	0.4		
December 20	73	4.5	0.2		
Case 20:					
December 12	30	2.6	3.0	500	Carcinoma of rectum, inoperable
December 15	39	3.0	2.2		
December 17	37	3.2	0.5		
December 19	38	2.7	0.2		Male, aged 57 years
December 22	35	2.5	0.1		
December 24	33	2.3	0.1		
December 27	34	2.2	0.1		

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Transfusion, cc.	Diagnosis and remarks.
Case 21:					
December 13	75	4.2	1.0	60	Malnutrition, pneumonia
December 15	80	4.3	0.4		
December 17	81	4.3	0.2		Male, aged 5 months
December 19	82	4.6	0.2		
December 20	...	...	...	80	
December 22	109	6.8	0.1	80	
December 23	110	6.5	0.1		
December 24	98	5.7	0.2		
December 26	123	6.5	0.1		
Case 22:					
December 8	30	1.4	1.2	350	Subleukemic myeloid
December 9	35	1.8	1.2		leukemia
December 11	36	2.0	1.2		
December 13	35	2.0	1.0		Male, aged 45 years
December 16	34	1.7	0.2		
December 18	35	2.1	0.4		
December 19	...	...	...	360	
December 20	44	2.9	0.2		
December 23	37	1.8	0.1		
December 26	35	1.7	0.1		
Case 23:					
December 23	36	2.2	0.6	300	Bleeding from cervix, pos-
December 24	38	2.9	0.2		sible carcinoma of cer-
December 27	40	2.7	0.3		vix, chronic nephritis
December 30	36	2.0	0.2		
January 2	40	2.2	0.2		Female, aged 39 years
January 6	40	2.4	0.3		
Case 24:					
December 9	53	3.0	0.4	500	Pneumonia
December 10	55	3.2	0.4		
December 12	59	3.5	0.3		Female, aged 2 years
December 15	59	3.4	0.6		
December 17	65	3.9	0.2		
December 19	68	3.9	0.1		
December 22	71	4.0	0.2		
Case 25:					
December 22	30	1.5	0.6	250	An aplastic anemia
December 23	33	1.6	0.4		
December 26	36	1.9	0.6		Male, aged 12 years
December 29	29	1.4	0.6		
December 31	30	1.5	0.7		Liver treatment begun
January 3	31	1.5	1.0	250	January 5
January 5	42	2.4	1.2		
January 10	42	2.4	0.6		
January 13	42	2.5	0.4		

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Diagnosis and remarks.
Control Case 1:				
December 29	51	3.2	1.0	Carcinoma of kidney
December 31	55	3.5	3.4	
January 3	62	4.1	4.0	Male, aged 37 years
January 7	61	4.0	0.8	
January 10	56	3.6	2.1	
January 12	58	4.1	1.0	

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Diagnosis and remarks.
Control Case 2:				
December 29	77	4.1	1.2	Chronic infectious arthritis
December 31	74	3.9	1.4	
January 3	79	4.3	0.8	
January 7	75	4.0	0.2	Male, aged 31 years
January 10	74	4.1	0.4	
January 12	76	4.2	0.7	
Control Case 3:				
December 29	60	3.5	0.1	Carcinoma of lung
December 31	63	3.8	0.1	
January 3	67	3.9	0.1	Male, aged 41 years
January 7	64	3.6	0.2	
January 10	59	3.5	0.1	
January 13	62	3.3	0.1	
Control Case 4:				
December 30	82	4.1	0.1	Acute appendicitis
January 2	84	4.4	1.4	
January 6	89	4.5	0.8	Female, aged 17 years
January 8	92	4.6	0.1	
January 9	89	4.5	0.1	Operation
January 12	90	4.3	0.1	
Control Case 5:				
December 30	77	3.9	1.0	Pneumonia
January 2	80	4.0	1.2	
January 6	80	4.1	0.2	Female, aged 30 years
January 8	82	4.4	0.6	
January 9	85	4.3	0.2	
January 13	87	4.5	0.1	
Control Case 6:				
December 30	67	4.1	1.2	Chronic ulcer of stomach
January 2	65	3.7	0.4	
January 6	73	4.0	1.0	Male, aged 60 years
January 8	70	3.5	1.4	
January 9	67	3.8	0.5	
January 13	71	4.1	1.0	

Discussion. From a study of the data presented, it is evident that large transfusions are followed by a drop in the reticulocyte percentage. Small transfusions are not followed by any definite rise in reticulocytes, which would suggest that their effect is similar to but less in degree than that of the large transfusions. A slight rise in reticulocytes, such as an increase of 0.5 to 1 per cent after transfusion means nothing, as the control cases show that this small variation in the reticulocyte percentage can occur from day to day in secondary anemia without transfusion, and moreover it is probably within the limit of error of this method.

As to the meaning of these findings, there are several possibilities. Transfusions may have some effect in improving maturation in the bone marrow, and the decrease of reticulocytes when associated with an increase in red blood cell count might thus be due to more mature red blood cells being formed. Then again, as Robertson[3] and Krumbhaar and Chanutin[4] have shown, the decrease in the

percentage of reticulocytes may reflect the lessened demand on the bone marrow because of the increased number of red cells temporarily available in the blood stream after transfusion. The latter interpretation, which seems the more plausible, would mean that transfusions are followed by a depression of bone-marrow activity.

In cases in which the bone marrow is exhausted, as in pernicious anemia, transfusions should be used with discretion and it is advisable for the clinician to consult with the transfusionist with regard to the amount of blood to be given.

Summary and Conclusions. 1. A series of 25 routine cases and 6 controls are presented in which the effects of blood transfusions on bone-marrow activity were studied. The percentage of reticulocytes in the peripheral blood was used as an index of bone-marrow activity.

2. An increase in the red blood cell count following transfusions is associated with a decrease in the percentage of reticulocytes.

3. This finding can be interpreted as meaning either (*a*) that transfusions aid in improving maturation of red cells in the bone marrow, or (*b*) (more likely) that transfusions by lessening the stimulus are followed by a depression of bone-marrow activity.

NOTE.—Grateful acknowledgment is due Dr. G. L. Rohdenburg, Director of the Laboratory, for his criticism of the manuscript, and Miss D. Green for technical assistance.

BIBLIOGRAPHY.

1. Hess, R.: Deutsch. Arch. klin. Med., 1909, **95**, 482.
2. Itami, S.: Fol. Haematol., 1908, **6**, 425.
3. Robertson, O. H.: J. Exp. Med., 1917, **26**, 221.
4. Krumbhaar, E. B., and Chanutin, A.: J. Exp. Med., 1922, **35**, 847.
5. Vogel, K. M., and McCurdy, U. F.: Arch. Int. Med., 1913, **12**, 707.
6. Minot, G. R., and Lee, R. I.: Boston Med. and Surg. J., 1917, **177**, 761.

PRIMARY HYPOCHROMIC ANEMIA (ERYTHRO-NORMOBLASTIC ANEMIA).

A NEW TYPE OF IDIOPATHIC ANEMIA.

BY WILLIAM DAMESHEK, M.D.,

INSTRUCTOR IN MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL, BOSTON, MASS.

(From the Medical Service and Department of Pathology, Beth Israel Hospital, Boston, Mass.)

THE observation recently of a group of patients with marked anemia whose clinical picture resembled in many respects pernicious anemia, but whose blood picture was that of a marked "secondary" anemia, resulted in an attempt at formulation of a new clinical entity, especially since treatment with iron rather than with liver

was effective in producing a remission. This condition I have called "primary hypochromic anemia."

With respect to nomenclature, the purely descriptive, almost naïve name "pernicious anemia" has been made archaic since the advent of liver therapy. As Schilling[1] has pointed out, the disease might more properly be called "megaloblastic hyperchromic anemia"—"megaloblastic" referring to the bone-marrow pathology which is characterized by the overproduction of megaloblasts (and macrocytes)—"hyperchromic" referring to the high color index, the individual red blood cell being filled with at least its normal complement of hemoglobin. This type of anemia has also been called "primary" because it is an anemia apparently arising *de novo* and comprising a distinct disease entity. Another of the "primary" types of anemias is "idiopathic" aplastic anemia which also is "hyperchromic" in that it exhibits a color indes of unity or above. The anemias secondary to various known causes, such as hemorrhage, infection, carcinoma and toxic conditions, however, are associated with a color index of less than unity—and are thus "hypochromic." Thus the concept has gradually developed that blood-pictures of anemia with hyperchromia and a color index of one or over are idiopathic and those showing hypochromia and a color index less than one are "secondary." That there are cases, however, in which hypochromia is present and yet the anemia is "primary" is not as yet generally recognized, so that even when no cause for the anemia can be found after diligent search, there is still the feeling that the anemia is not "primary" but secondary to some unknown cause.

In the last 2 years, several patients with a severe anemia for which no cause could be found, have been observed. This anemia was subject to spontaneous remissions and relapses, was associated with such symptoms as sore tongue and paresthesias, and showed objectively an atrophied tongue and (usually) achlorhydria. Hematologically, there was a "secondary" type of blood picture: *i. e.*, a low color index, hypochromia, and a diminished average red blood cell diameter. The anemia did not improve with liver therapy, but there was striking response to large doses of iron. In other words, it was felt that these patients were suffering from a form of "primary" anemia; and, since this anemia was associated with hypochromia rather than with the more common hyperchromia, it was called primary hypochromic anemia. In the course of the study of these patients, various relationships to Addisonian or pernicious anemia suggested themselves, resulting in the concept that there might be two types of pernicious anemia—the megaloblastic, associated with macrocytosis and hyperchromia, and the erythroblastic, associated with microcytosis and hypochromia. It is the purpose of this paper to bring out these possible relationships and to attempt to awaken interest in a hitherto but little recognized clinical entity.

The treatises on diseases of the blood make no mention of this form of anemia as an entity. Within the past year, however, there have been several reports of a similar type of hypochromic anemia under various names according to the author reporting it. Thus Kaznelson, Reiman, and Weiner[2] describe achylic chloranemia ("achylische chloranämie"), a term also used by Schulten.[3] Mills[4] calls it idiopathic hypochromic anemia. Altschuler[5] speaks of chronic hypochromic anemia ("anémie hypochrome chronique"). Faber[6] uses the terms simple anemia, simple hypochromic anemia, simple achylic anemia, and microcytic anemia. Wahlberg[7] mentions "simple anemias" associated with achylia. Castle[8] in all probability refers to this group of cases when he speaks of "chronic chlorosis." Mettier, Minot and Townsend[9] in their discussion of the treatment of the anemia of scurvy, refer to "anemias of ill defined origin particularly occurring in women and often associated with gastric anacidity." Witts[10] and Waugh[11] in recent articles, describe hypochromic anemias associated with achylia. It is thus seen that interest in this type of anemia is gradually increasing.

Report of Cases.—Our interest in this unusual type of anemia was stimulated by the case of Helen H. (Case 1 of the present series). After this case was studied, its relationship to other similar cases immediately suggested itself. These cases are the subject of the present report.

Case 1.—B. I. H., No. 7142. Helen H., a married housewife, aged 44 years, a native of Canada who had lived in New England for 4 years, was admitted to the Beth Israel Hospital of Boston on July 1, 1930, complaining of pallor and dyspnea on slight exertion. Family history was unimportant. Past history disclosed the following diseases: questionable rheumatic fever annually from the ages of 11 to 14; typhoid fever at 16; "malaria" about 10 years ago lasting for about a month, never recurring; an "inflamed right ovary" 9 years ago culminating in an operation for appendectomy and right oöphorectomy; influenza 6 years ago; and knowledge of a nodule in the thyroid gland for 5 years. Catamenia which began at the age of 12, had always been regular, lasting for 4 to 5 days. Ten years previously she weighed 160 pounds, but had gradually lost weight during the past 5 years so that on admission she weighed 121 pounds. Repeated questioning disclosed that the present illness began in reality about 5 years before admission. At that time, she became markedly pale, weak, dyspneic on the slightest exertion, had 3 to 5 loose movements daily, and lost 30 to 40 pounds in weight. She was at that time in St. John, New Brunswick, where she consulted a doctor who told her she was "anemic" and gave her "iron pills" of which she used 100. Her color and strength gradually returned and she gained 20 pounds in weight. However, 4 years previously she again developed the above symptoms, again took the same iron pills, and was again relieved. She then felt well until 2 years before admission when the identical symptoms of weakness, pallor, loss of weight, and diarrhea recurred. She had by now lost her iron prescription and did not consult a doctor. A year and a half ago, she developed increased menstrual flow and at times would flow between periods. The symptoms were at their worst in December, 1929. At this time, her tongue became markedly sore so that she was unable to eat oranges or any other "acid" fruits or vegetables; she consulted a doctor about this and was given a mouth wash with but little relief. After this, she developed numbness and tingling

of the fingers and toes. Pallor gradually grew worse; she again had 3 to 5 loose bowel movements daily; she could hardly drag herself about and was dyspneic even on walking across the floor. She finally came to the Boston Dispensary in June, 1930, and was referred to the Beth Israel Hospital for study. At no time had she taken any drugs other than those mentioned above. Appetite was extremely poor but she ate meat, green vegetables and fruits in moderate amounts. Her ordinary dietary was: breakfast—toasted white bread, cereal, coffee or tea; luncheon—bacon, egg, potato, tea or coffee; supper—stew (vegetables, meat), green vegetable salad, pie. She had 2 oranges and 2 glasses of milk daily.

Physical examination on admission showed a well-built but very thin woman with extreme pallor. She weighed 121 pounds. The skin color seemed at first glance yellowish, but this was found to be due to the extreme pallor of the tissues rather than to icterus. The scleræ showed no icterus whatever. The patient's eyes were brown in color, as was the hair. The tongue was smooth, atrophied, and without coat; there was some redness at the edges. The buccal mucosæ were very pale. A firm nodule, the size of a walnut, was present in the right lobe of the thyroid gland. There was a soft systolic murmur over the precordium; otherwise the heart showed nothing abnormal. The liver edge was felt 1 to 2 fingers' breadth below the right costal margin; the spleen was not felt except once by one observer. The reflexes showed the following: exaggerated Achilles bilaterally; radials, biceps and triceps equal and active. The left knee jerk was present, though sluggish; the right absent. A definitely positive Babinski test was present on the left, absent on the right. There was no ankle clonus. Vibratory sensation was undisturbed; there was some hyperesthesia of the lower extremities. The uterus was slightly enlarged but showed no evidence of fibromyomata or disease of the cervix. Blood pressure was 115 systolic, 50 diastolic. Temperature was 99.8° F. in the afternoon.

Laboratory examinations were as follows: Wassermann, Kahn, and Hinton tests negative; gastrointestinal Roentgen ray series negative except for questionable adhesions in the right lower quadrant of the abdomen; barium enema negative; plain plates of the kidneys, ureters, and bladder negative; cholecystograms by the dye method negative; Roentgen rays of all the long bones, vertebræ, skull, and chest negative. A large number of urine specimens were normal; four stools showed no occult blood. Icteric index was 4. Gastric analysis with 7 per cent alcohol test meal followed in 45 minutes by 0.5 mg. of histamin in solution showed no free hydrochloric acid 1 hour after histamin was given and a total acidity of 4 at the same period; the volumes of gastric juice obtained were exceedingly low. Blood studies on July 1 and 2 showed the following: hemoglobin, 20 per cent (Dare and Sahli); red blood cell count, 2.7 and 2.3 million per cu. mm.; white blood cell count, 3700 and 4050 per cu. mm.; polymorphonuclears, 45 per cent; lymphocytes, 51 per cent; monocytes, 0; eosinophils, 4 per cent; basophils, 0. Red blood cells showed very marked achromia, extreme change in size and shape with small cells predominating and little or no polychromatophilia. Average red blood cell diameter was 6.02 micra, the cells varying from 3 to 7 micra. The blood platelet count was 154,000 per cu. mm. by a pipette method—267,000 per cu. mm. by the author's indirect method.* Reticulocytes numbered 0.7 per cent. The remainder of the blood counts are given in Table I.

Bone-marrow Biopsy. A biopsy of the sternal bone-marrow was performed on July 10. This showed an exceedingly hyperplastic marrow. It was crowded with large numbers of nucleated red cells, the white blood cell forming elements being diminished. The characteristic feature of the

* To be published. It involves the use of a stain for making the blood platelets visible and counting them under oil immersion.

TABLE 1.—CASE 1. HELEN H.

Date.	Hemoglobin, per cent; D = Dare, S = Sahli.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Platelets, per cu.mm.; I = indirect, D = direct method.	Reticulocytes, per cent.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.	Dosage and remarks.
July 1, 1930	20 (D)	2.7	3700	....	..	9	90	1.0	0	0.0	
July 2, 1930	15 (S)	2.47	3200	I 267,000 D 154,000	0.7	43	44	13.0	..	..	Achromia +++; anisocytosis +++; poikilocytosis +++; polychromatophilia 0; 3 normoblasts seen in counting 100 white blood cells; platelets appear slightly decreased; average red blood cell diameter = 6.02 micra.
July 5, 1930	20 (D)	2.3	3600	....	..	38	54	2.0	5	1.0	
July 8, 1930	15 (S)	1.88	6300	I 488,800 D 376,000	2.0						
July 10, 1930	18 (D)	2.8	6700	....	3.4	..	...	..	..	..	Liver extract, 4 vials daily begun.
July 14, 1930	13 (S)	2.46	2900	I 442,000 D 182,000	1.8						
July 15, 1930	20 (D)	2.9	....	....	5.2						
July 16, 1930	13 (S)	2.26	2600	I 248,000 D 226,000	0.6	..	...	..	...	..	Anisocytosis ++++, with microcytes—occasional fairly large cells; poikilocytosis +++; polychromatophilia; platelets often large and bizarre.
July 17, 1930	20 (D)	2.9	....	....	4.6						
July 18, 1930	15 (S)	3.22	3400	I 483,000 D 264,000	2.4						
July 20, 1930	15 (D)	2.68	....	....	3.2	..	...	..	..	..	Liver extract discontinued.
July 21, 1930	15 (S)	1.96	5100	I 250,000 D 164,000	5.8	..	...	..	..	..	Ferric and ammonium citrate 3 gm. daily begun.
July 30, 1930	35 (S)	2.91	5600	I 465,000 D 340,000	6.7						
August 2, 1930	37 (S)	3.38	4600	I 255,000 D 254,000	6.4	64	21	8.0	6	1.0	Achromia ++; marked anisocytosis with good many large cells well filled with hemoglobin; poikilocytosis ++++; polychromatophilia ++.
August 5, 1930	40 (S)	3.17	4600	I 348,700 D 232,000	0.8	..	...	..	..	..	Ferric and ammonium citrate 6 gm. daily; average red blood cell diameter 5.94 micra; achromia ++; anisocytosis +++; polychromatophilia 0.
August 9, 1930	46 (S)	3.95	....	I 1,169,000 D 424,000	9.6						
August 13, 1930	51 (S)	3.99	6000	I 1,707,000 D 458,000	2.8						
August 18, 1930	56 (S)	4.36	6500	I 506,000 D 206,000	1.0						
August 30, 1930	63 (S)	4.86	5500	I 602,000 D 252,000	1.2	51	25	14.5	9	0.5	
September 6, 1930	77 (S)	4.45	6400	I 489,000 D 300,000	1.0						
October 29, 1930	88 (S)	4.64	6500	I about 2,000,000	0.0						

marrow was the large number of erythroblastic islands composed of cells about 1½ the size of the normoblast, with a grayish, fairly abundant cytoplasm and a round nucleus which contained coarse masses of chromatin. Numerous transitions between these erythroblasts and the typical normoblasts were seen. No megaloblasts were found.

Clinical Course. On admission, the patient was given a 4000 calorie diet with liver. However, she ate only about one-half of this so that during her stay in the hospital, she gradually lost weight. Liver was discontinued after the first day. The afternoon temperature was constantly elevated to 99.8° F., the pulse ranging between 80 to 100 per minute. Beginning with July 10, she was regularly given 4 vials of liver extract daily (Lilly No. 343) until July 20 without clinical or hematologic improvement. In fact, the anemia, especially the percentage of hemoglobin, became slightly more severe during this period, as shown on Chart I. On July 21, she was discharged from the hospital against advice. Before discharge, however, she was advised to take ferric and ammonium citrate in doses of 1 gm. 3

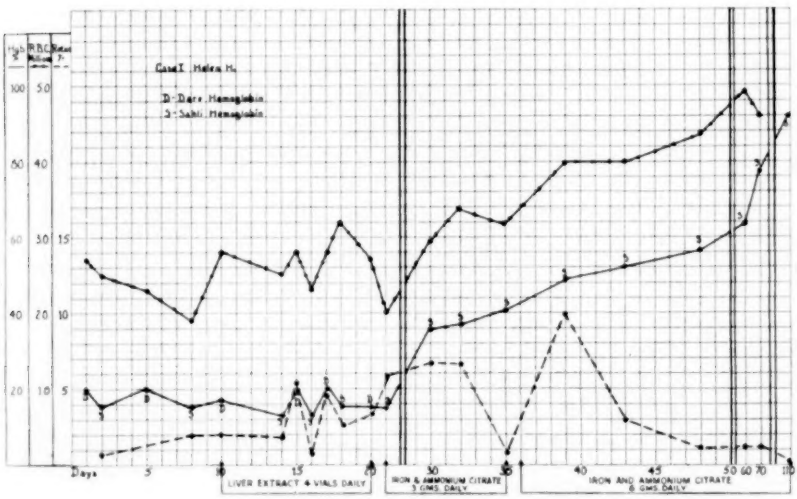

Case I Helen H.
D=Dare Hemoglobin
S=Sahli Hemoglobin
Days
LIVER EXTRACT 4 VIALS DAILY
IRON & AMMONIUM CITRATE 3 GMS. DAILY
IRON AND AMMONIUM CITRATE 6 GMS DAILY

CHART I.

times daily (in 25 per cent aqueous solution), and to continue with her regular diet. On July 21, the date of discharge, hemoglobin was 15 per cent; red blood cell count, 1,960,000 per cu. mm.; white blood cell count, 5100 per cu. mm. She returned to the blood clinic on July 30, 9 days after discharge. She had felt no change for 3 days after starting the iron. However, on the fourth day, she awoke feeling a great deal better and with a desire to eat. She began to eat ravenously on that day and continued to do so. Her tongue became less sore and the numbness and tingling of the fingers became diminished. There had been a marked rise in hemoglobin and erythrocyte count in this 9-day period, hemoglobin having risen from 15 per cent to 35 per cent and the red blood cell count almost a million per cu. mm. The reticulocytes were increased to 6.7 per cent, but it is probable that the height of the reticulocyte response had been passed. Polymorphonuclear and platelet counts had also shown a definite increase. In the next few days, there was but little change: as a matter of fact, the leukocyte and platelet counts had fallen. The dosage of ferric and ammonium citrate

was therefore doubled to 6 gm. daily. In a week there was another marked response, so that on August 9, hemoglobin was 46 per cent, erythrocyte count 3,950,000 per cu. mm. Blood platelets had reached the astonishing level of 1,200,000 per cu.mm. and reticulocytes numbered 9.6 per cent. Her tongue bothered her no longer; she could now tolerate even vinegar. There were no paresthesias. Appetite continued to be ravenous so that she ate almost constantly. There was no weakness or dyspnea. She was gaining considerable weight, and her color was now quite pink. She said that she now felt better than she had for years. From that time on there was continued clinical and hematologic improvement. On October 29, hemoglobin was 88 per cent; red blood cell count, 4,640,000 per cu. mm.; white blood cell count, 6500 per cu. mm.; blood platelet count, 600,000 per cu. mm.; reticulocytes, 0 per cent. She had voluntarily discontinued iron therapy about a month previously. There was remarkable clinical improvement. Her face was extremely red, almost plethoric. She was now quite robust, her weight being 158 pounds.

Summary of Case 1. A woman aged 44 developed in 1925 dyspnea, weakness, loss of weight, diarrhea and marked pallor; she was found by a doctor to be anemic, was given iron and became much improved. In 1926, however, the symptoms recurred, but she again took iron and again became improved. In 1928, there was a third relapse; she took no iron at this time, however; symptoms became progressively worse so that in December, 1929, she could hardly walk about. At this time she developed marked soreness of the tongue and paresthesias of the fingers and toes. In July, 1930, she came to the Beth Israel Hospital for treatment. She presented a very severe anemia of the "secondary" type for which, however, no cause could be found. Tongue was smooth; there were signs of "combined system disease." Gastric analysis showed no free hydrochloric acid even after histamin. Bone-marrow biopsy disclosed crowding of the marrow with erythro- and normoblasts. The erythroblasts were present in islands. There was no response to liver extract. On taking large doses of iron and ammonium citrate there was immediate and striking response so that in the course of 3 months she became entirely well. Hemoglobin rose in this period from 12 to 88 per cent; red blood cell count from 1,960,000 to 4,640,000 per cu. mm.; white blood cell count from 3200 to 6500 per cu. mm. There were definite reticulocyte and platelet responses.

It was felt that this patient had pernicious anemia, although of an unusual type. The subjective symptoms were typical of that disease, *i.e.*, recurring anemia associated with diarrhea, anorexia and weakness, sore tongue, paresthesias. Except for the lack of icterus which in the ordinary type of pernicious anemia is due to break-down of red blood cells, the objective signs were also typical: extreme pallor, a very smooth tongue with atrophied papillæ, and the signs of "combined system disease." The gastric analysis with its lack of free hydrochloric acid after histamin was typical. The blood studies showing anemia, leukopenia, relative lymphocytosis, monocytopenia, and slight thrombocytopenia were consistent with

the ordinary case of pernicious anemia. However, the red blood cells were smaller than normal and poorly filled with hemoglobin—in other words, there was microcytosis with hypochromia and a color index under 1 as opposed to ordinary pernicious anemia in which there is macrocytosis and hyperchromia and a color index over 1. The bone-marrow, despite the anemia was crowded with erythroblasts and normoblasts: this too was reminiscent of the bone-marrow of pernicious anemia, which despite the anemia is crowded with megaloblasts. For reasons cited below, it was felt that this patient had pernicious anemia, but of an unusual type—dependent upon an erythronormoblastic or normal response of the marrow rather than upon a megaloblastic or embryonic response.

Case 2.—B. I. H., No. 971. J. W., a married pipe fitter, aged 29 years, a native of this country (Maine) was admitted to the Beth Israel Hospital for study of his anemia on December 19, 1928. Family history was unimportant; he was separated from his wife. Born in Maine, he had always lived in New England. Until recently he had been a pipe fitter but had lately become a metal worker and occasionally came in slight contact with lead. Six years previously he had contracted gonorrhea and shortly thereafter developed "rheumatism." In March, 1927, while working in Berlin, New Hampshire, he developed "grippe," which was followed by increasing weakness, loss of weight and pallor. He consulted a doctor who told him he was anemic and gave him subcutaneous injections. Anemia persisting, however, he consulted in October, 1927, another physician who found he "had no blood at all." This physician in writing to the Beth Israel Hospital in 1928, said that the patient "presented the characteristic symptoms of pernicious anemia with the typical blood picture." He accordingly gave the patient liver, iron pills and acid, with resultant rapid improvement in both the subjective symptoms and the anemia. Hemoglobin rose from 35 to 85 per cent. For about a year the patient felt better, but during October, 1927, he again developed weakness, dyspnea, severe headache, loss of weight, lack of color, and pulling sensation in the legs. These symptoms rapidly grew worse so that he finally came to the Boston Dispensary and was referred to the Beth Israel Hospital for study. He gave no history of bleeding from any source, nor had he varied in his dietary habits, which were normal. On examination he was found to have white pallor, no icterus being present. The eyes were brown, the hair of the same color. The lower eyelids were slightly puffy. Tongue was smooth, the papillæ at the edges atrophied. Lungs were normal. Heart, except for a heaving impulse and a soft blowing systolic murmur at the apex, was normal. Blood pressure was 128 systolic, 68 diastolic. Neither liver nor spleen were felt. Lymph nodes were not enlarged. The reflexes were normal.

Laboratory Data. The blood showed a marked degree of "secondary" anemia: *i. e.*, hemoglobin was 42 per cent (S); red blood cell count, 3,470,000 per cu. mm.; color index, 0.67; white blood cell count, 4400 per cu. mm.; blood platelets, 100,000 per cu. mm.; reticulocytes, 0.8 per cent. The red blood cells showed marked achromia with many microcytes; average red blood cell diameter was 6.14, variation from 3.6 to 8.0 micra. There was considerable poikilocytosis, but no polychromatophilia or basophilic stippling. One normoblast was seen in counting 100 leukocytes. The polymorphonuclear cells numbered 59 per cent, lymphocytes, 23 per cent; monocytes, 11 per cent; eosinophils, 3 per cent, and basophils, 4 per cent. Blood platelets seemed diminished on blood smear.

TABLE 2.—CASE 2. JAMES W.

Date.	Hemoglobin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Blood platelets, per cu.mm.	Reticulocytes, per cent	Polymorphonuclear cells, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.	Dosage and remarks.
December 20, 1928	40 (T)	3.21	7,050	....	...	62	20	16	2		
December 21, 1928	42 (S)	3.47	4,400	100,000	0.8	59	23	11	3	4	
December 23, 1928	...	...	...	....	...	72	20	8	...	...	Liver, ½ pound daily.
December 26, 1928	60 (T)	3.7	7,000	120,000	3.4	...	...	...	...	...	Ferrous carbonate, 1 gm. daily.
December 28, 1928	...	...	...	....	...	...	...	...	...	...	Liver extract (Lilly No. 343), 5 vials daily.
December 31, 1928	60 (T)	4.39	...	....	2.8						
January 2, 1929	70 (T)	4.4	9,200	....	3.8						
January 4, 1929	...	4.63	10,700	....	...	76	16	4	4		
January 8, 1929	70 (T)	5.2	9,600	....	...	76	16	6	2		
January 9, 1929	85 (T)	...	...	....	3.6						
January 13, 1929	80 (T)	5.1	9,400	....	...	71	17	9	3	...	Weakness and pallor developed in August, 1930; liver, ½ pound daily, August 3, 1930 to September 2, 1930.
September 2, 1930	38 (S)	3.8	5,600	....	...	56	32	8	2	2	Iron and ammonium citrate, 8 gm. daily.
September 6, 1930	46 (S)										
September 13, 1930	72 (S)	4.8									
September 20, 1930	74 (S)										
September 27, 1930	82 (S)	5.4	...	....	...	76	16	6	2	...	Iron and ammonium citrate taken intermittently.
November 1, 1930	65 (T)	4.6									

Roentgen rays of the chest, sinuses, kidneys, teeth and gastrointestinal tract were all negative. Several urines were negative as were several stools tested for occult blood. The blood and spinal fluid Wassermann reactions were negative. Mosenthal test showed normal variation in specific gravity; phthalein excretion was 40 per cent in 2 hours. The spinal fluid was entirely normal. The basal metabolic rate was + 10 per cent. Gastric analysis on December 23 showed no free hydrochloric acid in the fasting contents, but 45 minutes after a test meal, 24 units of free hydrochloric acid was present.

Bone-marrow biopsy (sternum) was performed on December 31, 1928. This showed crowding of the marrow with erythro- and normoblasts, about 5 nucleated red cells to each white cell (normal about 1 to 1) being present. Only a few questionable megaloblasts were seen.

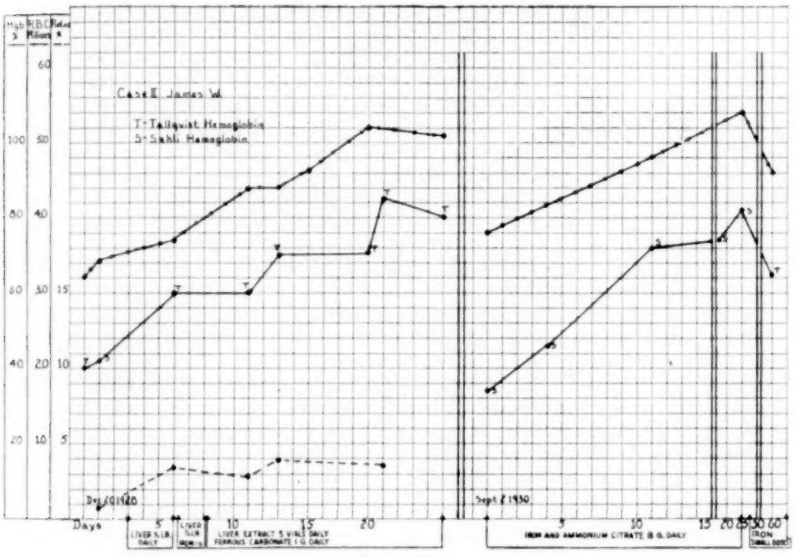


CHART II.

Clinical Course. It was originally felt that the anemia was secondary to some disorder such as hypothyroidism, nephritis, chronic infection, malignancy, etc., but apparently all of these possibilities were ruled out by the above findings. The suggestion was raised at that time by the author as to whether this might not be "a primary anemia of a secondary type (chlorosis?)."

On December 23, 1928, the patient was started on about ½ pound of liver daily in addition to the regular house diet. On December 26, he was given in addition ferrous carbonate 1 gm. daily. On December 28, liver was discontinued (the iron still being retained), and he was given 5 vials of liver extract (Lilly's No. 343) daily. It was difficult at the time to evaluate which of these methods of treatment was responsible for the subsequent rapid improvement. The patient rapidly improved, as will be seen from Chart II and was discharged from the hospital on January 15, 1929. At this time hemoglobin was 80 per cent (T); red blood cell count, 5,100,000 per cu. mm.; white blood cell count, 9400 per cu. mm.; polymorphonuclears, 71 per cent. There had been slight reticulocyte rise.

He was not heard from until almost 2 years later, when, on September 2, 1930, he was referred to the author for treatment of his anemia. He had felt well until August, 1930, at which time he developed a slight urethral discharge. This was treated by a physician with prostatic massage and silver nitrate irrigations of the bladder with subsequent relief. However, he soon developed aching pain in numerous muscles and became rapidly weak, pale, listless, and dyspneic. Frontal headache was intense. He claimed his appetite was poor, yet he managed to eat daily the following breakfast—two eggs, oatmeal, milk, toast, coffee; lunch—sandwiches, fruit; supper—soup, meat, green vegetables, pastry. He had lost a few pounds in the past few weeks. Weakness forced him to quit work. Examination was negative except for marked pallor, some stiffness of the dorsal spine, and smoothness of the tongue. Hemoglobin was 38 per cent (S); red blood cell count, 3,800,000 per cu. mm.; white blood cell count, 5600 per cu. mm. For 3 weeks prior to consulting the writer, he had been eating at least a ½ pound of liver daily, but despite this had been growing progressively weaker and paler. He was accordingly advised to discontinue the liver and to take ferric ammonium citrate in doses of 2 gm., 4 times daily (8 gm. daily). He began to take this medication on September 3. He awoke on the morning of September 5, feeling much better, "different." His appetite became ravenous so that after eating a large "steak supper," he again felt hungry in 2 hours. His blood picture improved almost miraculously, the hemoglobin rising in 3 days to 46 per cent, in 11 days to 72 per cent, in 25 days to 82 per cent. The headache, weakness, dyspnea, pallor disappeared quickly, but the patient complained bitterly of pains in his joints. The spine was quite stiff ("poker spine"), as was the lower back. He was accordingly given 3 injections of typhoid vaccine intravenously at weekly intervals. Although these gave transient relief, there was very little permanent response. On November 1, 1930, he looked rather poorly. Arthritis had been severe, preventing sleep at times. Tongue had become sore in the past 2 weeks. He had been taking the iron medication rather irregularly, from 2 to 6 gm. daily. There was some weight loss (to 134 pounds). Hemoglobin was 65 per cent (T), a distinct drop. Heat, massage, physiotherapy, etc., were advised.

Summary of Case 2. A 29-year-old American developed severe anemia (said to be pernicious anemia) in 1927. This was treated with liver and iron, with recovery. In 1928, there was a relapse of anemia. Examination disclosed a "secondary" type of anemia: hemoglobin, 42 per cent; red blood cell count, 3,470,000 per cu. mm.; white blood cell count, 4400 per cu. mm.; hypochromia and an average red blood cell diameter of 6.14 micra. No cause for this "secondary" anemia could be found. Gastric analysis showed free hydrochloric acid after a test meal. Bone-marrow biopsy, despite the anemia, disclosed crowding of the marrow with erythro- and normoblasts. There was prompt response to a mixed treatment of liver, iron, and liver extract. The patient felt well for almost 2 years, but again became weak, dyspneic and pale in August, 1930. On September 2, blood showed hemoglobin, 38 per cent; red blood cell count, 3,800,000 per cu. mm. He had been taking at least ½ pound of liver daily for 3 weeks; in spite of this pallor had been growing steadily worse. Liver was discontinued and he was given iron and ammonium citrate in doses of 8 gm. daily. There was prompt response, so that

on September 27 (24 days after beginning treatment) hemoglobin was 82 per cent and red blood cell count was 5,400,000 per cu. mm. However, although his strength, color and appetite became normal, arthritis persisted, preventing sleep at times. He lost weight, developed a sore tongue, took his medication irregularly. On November 1, 1930, hemoglobin was 65 per cent (T), and red blood cell count 4,600,000 per cu. mm. In this case, then, there were 3 relapses of severe anemia which, during the first relapse was considered to be "pernicious," during the second, was thought to be a peculiar type of "secondary" anemia, but which was at the third relapse considered to belong to a disease entity closely resembling pernicious anemia clinically, and probably an unusual type of pernicious anemia with a normoblastic rather than a megaloblastic marrow.

Case 3.—B. I. H., No. 3254. B. S., a housewife, aged 23 years, a native of Russia, was admitted to the Beth Israel Hospital on July 26, 1929, for study of anemia. Family history was unimportant. She said she had been more or less pale since infancy and had never been very strong. She had had since infancy attacks of diarrhea which were ordinarily associated with marked pallor. At the age of 15 she was admitted to a Russian hospital for study of anemia which was associated with a "big stomach." She was given 16 subcutaneous injections, and medicine by mouth. Pallor disappeared within the course of 2 months. However, a year later, being faced with a good deal of housework, she again became pale, again entered the same hospital, and was again relieved. She was well from that time until 6 months after the birth of her first child in January, 1929, when she again became weak, pale, and increasingly dyspneic. Her appetite became very poor. There was occasional tingling of the fingers but no burning of the tongue. Examination disclosed marked pallor. The tongue was smooth at the edges, the papillæ not being visible. The liver was questionably felt at the right costal margin; the spleen was not felt. Skin showed fairly numerous ecchymoses and petechiæ. Reflexes were normal.

Laboratory Data. On admission hemoglobin was 35 per cent (T); red blood cell count, 2,100,000 per cu. mm.; white blood cell count, 3240 per cu. mm.; polymorphonuclears, 54 per cent; lymphocytes, 40 per cent; monocytes, 5 per cent; eosinophils, 1 per cent. On July 30 the blood platelets were much reduced, being 44,000 per cu. mm., by a pipette method and 56,280 per cu. mm., by the author's indirect method. Reticulocytes numbered 1.5 per cent; polymorphonuclears were 30 per cent; lymphocytes, 54 per cent; monocytes, 9 per cent; eosinophils, 5 per cent; basophils, 2 per cent. The red blood cells showed extreme change in size with many microcytes; average erythrocyte diameter was 5.72 micra, variation from 3 to 10 micra. There was marked achromia, marked change in shape and slight polychromatophilia. The blood platelets were much reduced on blood smear. Bleeding time was 12.5 minutes, definitely increased; coagulation time 2¼ minutes; clot retraction was fair. Fragility test was within normal limits—hemolysis beginning at 0.46 per cent of sodium chlorid and being complete at 0.36 per cent. Several urines and stools were normal. The Mosenthal test showed good variation in specific gravity. Icteric index was 4. Gastric analysis showed no free hydrochloric acid in the fasting contents; 1 hour after a test meal there was 1 unit of free hydrochloric acid present, total acidity being 8. Gastrointestinal Roentgen rays showed at first an irregular duodenum suggesting ulcer, but after the subcutaneous

TABLE 3.—CASE 3. BESSIE S.

Date.	Hemoglobin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Blood platelets, per cu.mm.	Reticulocytes, per cent.	Polymorphonuclear cells, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.	Dosage and remarks.
July 26, 1929	35 (T)	2.1	3240	.....	...	54	40	5	1		
July 29, 1929	...	2.5									
July 30, 1929	...	2.68	...	I 56,280 D 44,000	1.5	34	54	5	5	2	
August 1, 1929	...	2.7									
August 4, 1929	...	...	...	.....	...	...	...	...	...	...	Iron and ammonium citrate, 6 gm. daily begun.
August 7, 1929	...	2.49	...	.....	6.0	59.5	31.5	3.5	3.5	2	
August 10, 1929	...	...	8150								
August 11, 1929	...	...	...	I 1,375,000	4.8	54	33	8	4	1	Crowded with platelets.
August 12, 1929	41 (8)	2.87	5040	.....	...	70	22	6	1	1	
August 19, 1929	46 (8)	3.38	4320	.....	...	62	29	6	3	0	
August 23, 1929	...	...	6550								
September 6, 1929	60 (8)	3.41	6400								
September 20, 1929	60 (8)	3.415	6200	.....	...	...	...	...	...	...	Iron discontinued.
October 4, 1929	45 (8)	3.1	7500	.....	...	38	42	12	6	2	Reduced iron 4 gm. daily.
November 1, 1929	40 (8)	4.27	...	I 884,000 D 395,000	0.4	...	...	...	...	...	Liver, ½ pound daily, and iron.
November 15, 1929	45 (8)	4.58	...	I 343,000 D 154,000	1.2	40	35.5	13.5	10	1	
December 6, 1929	48 (8)	...	...	D 248,000							
December 27, 1929	46 (8)	4.6	...	I 1,228,000 D 774,000	0.9	52	27.5	11.5	8	1	
January 24, 1930	50 (8)	4.59	...	I 927,000 D 378,000	0.6						
April 18, 1930	52 (8)	4.55	...	I 428,000 D 262,000	...	...	...	...	...	...	Iron almost completely discontinued.
May 21, 1930	43 (8)	4.16	...	I 407,000 D 320,000	0.4	...	...	...	...	...	Iron discontinued.
November 12, 1930	45 (8)	4.05	...	I 810,000	1.3	...	...	...	...	...	Iron and ammonium citrate 3 gm. daily.
February 18, 1931	55 (8)	4.21	...	.....	...	...	...	...	...	...	Iron and ammonium citrate 3 gm. and copper sulphate 0.1 gm. daily.
April 16, 1931	68 (8)	4.75	...	.....	...	...	...	...	...	...	Copper sulphate 0.05 gm. daily. Iron same dose.
July 21, 1931	82 (8)	5.25									

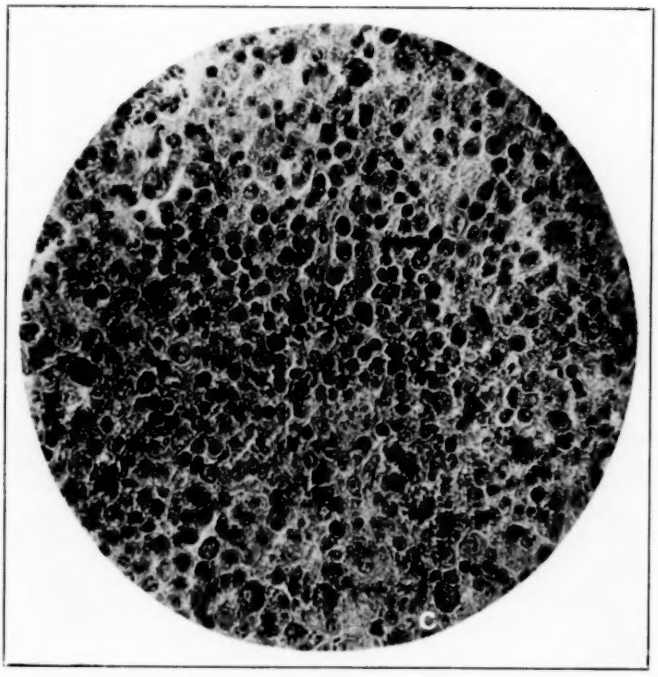


FIG. 1.—(C)—Photomicrograph of sternal bone-marrow biopsy. Case 1, July 10, 1930. × 600. Note the exceedingly hyperplastic marrow despite the extreme anemia (hemoglobin 15 per cent, red blood cell count 2,000,000). The large majority of the cells are pale staining erythroblasts, among which are interspersed the more mature normoblasts with pyknotic nuclei.

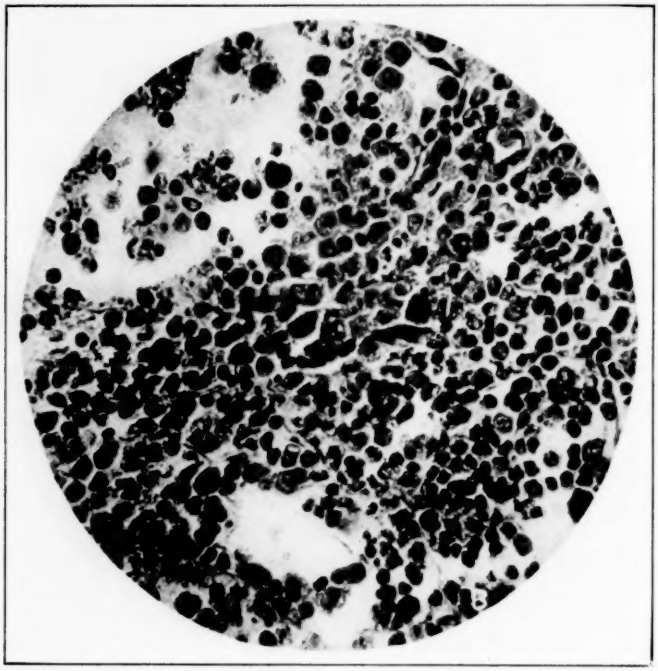


FIG. 2.—(*B*)—Photomicrograph of sternal bone-marrow biopsy. Case 1, July 10, 1930. × 600. Note the large numbers of normoblasts. In the upper right portion of the field is an island of white cell-forming tissue.

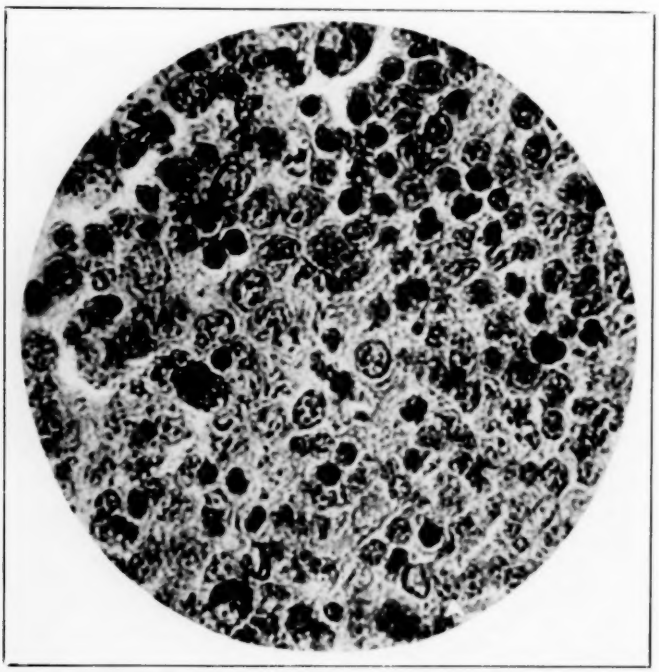


FIG. 3.—(*A*)—Photomicrograph of sternal bone-marrow biopsy. Case 1, July 10, 1930. × 1200. Numerous normoblasts and large numbers of pale staining, more primitive, nucleated red cells, *i. e.*, erythroblasts.

injection of atropin this irregularity disappeared leading to a roentgenologic diagnosis of a normal gastrointestinal tract. Bone-marrow biopsy on July 31, 1929, disclosed, despite the severe anemia, a marrow crowded with erythro- and normoblasts, many more being present than normally. Three hundred nucleated red cells were seen simultaneously with 160 white cells, a ratio of 3 to 1.6, abnormally high (normal about 1 to 1). Of these nucleated red cells, 59.3 per cent were normoblasts, 37.0 per cent erythroblasts, and 3.7 per cent megaloblasts. Two megakaryocytes were seen in this count.

Clinical Course. On August 4, 1929, iron and ammonium citrate in doses of 2 gm., 3 times daily were begun. This resulted in rapid clinical and hematologic improvement. Reticulocyte count, white blood cell count, polymorphonuclear count, platelet counts all showed prompt rises. On August 7, although there was no rise in red blood cell count, reticulocytes had risen to 6 per cent and blood platelets were now very abundant. On August 11, the blood smears were found crowded with platelets; on actual count they numbered 1,375,000. Ecchymoses and petechiæ

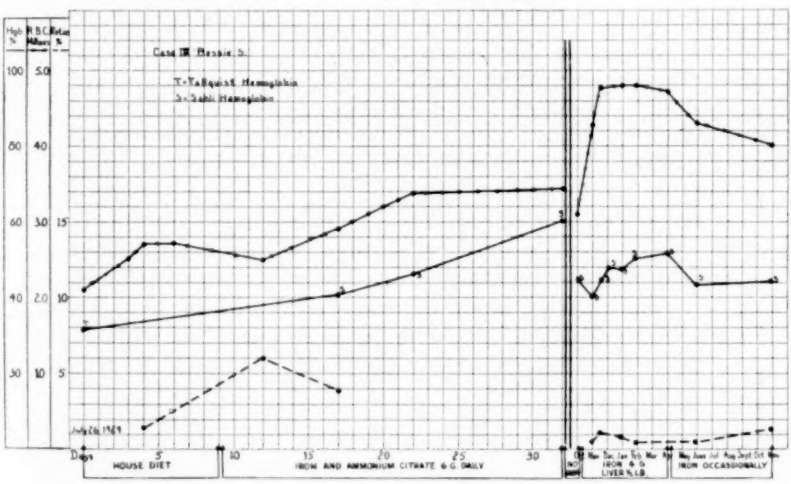


CHART III.

promptly disappeared. Soon there was rise in both hemoglobin and red blood cell count, so that on September 6, hemoglobin was 60 per cent (T), and red blood cell count 3,410,000 per cu. mm. She returned in October, however, feeling rather poorly again; she had discontinued the iron solution to great extent because of a dislike for its taste. She was accordingly given reduced iron in doses of 2 gm. twice daily, and later advised to eat ½ pound of liver daily. There was fairly good response to this therapy from that time on until the following spring, although the red blood cell count showed a much greater rise than did the hemoglobin which persisted at about 50 per cent. On May 21, 1930, she showed again a definite drop in counts and was advised again to continue with iron medication which she had almost completely discontinued. She was not seen again until November 12, 1930, when she again came to the clinic. She had discontinued iron medication several months previously. Hemoglobin had again dropped. Iron was again begun but without much change in counts. When copper sulphate was combined with the iron medication, there was striking response.

Summary of Case 3. A woman, aged 23 years, had been pale since infancy. From the ages of 1 to 13 she had been subject to relapses of diarrhea and pallor. At 15 and 16 years of age she had severe relapses of anemia, necessitating treatment in a hospital. In July, 1929, 6 months after delivery of her first child, she became weak, dyspneic, and pale. Examination disclosed a very pale woman without icterus and with smooth atrophied tongue. Ecchymoses and petechiae were common. Blood showed a marked "secondary" type of anemia; hemoglobin was 35 per cent (T); red blood cell count was 2,100,000 per cu. mm.; white blood cell count 3240 per cu. mm. There was relative lymphocytosis and marked reduction in blood platelets with increase in bleeding time. No cause could be found for this "secondary" anemia. Gastric analysis showed almost no free hydrochloric acid after first test meal. Bone-marrow biopsy disclosed a hyperplastic marrow crowded with erythro- and normoblasts despite the severity of the anemia. There was striking response to iron therapy in large doses, but when this was discontinued there was definite relapse which was checked by further iron therapy. She took iron medication very irregularly and there were definite relapses. Liver therapy combined with the iron at one time seemed to aid erythrocyte response. The percentage of hemoglobin tended to remain stationary at about 50 per cent. Upon the addition of copper sulphate, hemoglobin rose steadily to 82 per cent. Remissions were accompanied by definite increases in reticulocytes and outpouring of platelets in large numbers. It was felt that this was another instance of primary hypochromic anemia, and possibly a type of pernicious anemia associated with an erythronormoblastic marrow rather than with one of the ordinary megaloblastic type.

Case 4.—O. P. D., No. 11799. Mary C., a housewife, aged 37 years, a native of Scotland, came to the outpatient department on May 15, 1930, complaining of weakness which had been present since January, 1930. Family history was unimportant. She had been married 15 years, her husband and 3 children being alive and well. She had been well until 1923 when a miscarriage occurred. At that time she became pale, although the loss of blood was slight. Chronic backache developed. In 1929 she developed numbness and tingling of the fingers and numbness of the entire face, especially on the right. Her appetite had always been quite poor. She claimed that meat made her choke. As a result she had not eaten meat for 10 years or more, her dietary otherwise being satisfactory. She admitted being of the nervous type, easily irritated, easily worried. Examination disclosed a light-haired, blue-eyed woman. Tongue was atrophied, being very smooth and glistening throughout. A soft systolic murmur was heard over the mitral area. The spleen was felt by one observer. The finger-nails showed definite "trophic" changes, being markedly cracked and deformed. Reflexes were normal; vibratory sensation was definitely diminished over the left leg, normal elsewhere. Blood pressure was 128 systolic and 75 diastolic. Gastric analysis showed no free hydrochloric acid in the fasting contents; 1 hour after Ewald test meal there was a faint trace of free hydrochloric acid, not enough to titrate. Blood Wassermann reaction

TABLE 4.—CASE 4.—MARY C.

Date.	Hemoglobin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Blood platelets, per cu.mm. I = indirect, D = direct.	Reticulocytes, per cent.	Polymorphonuclear cells, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils per cent.	Basophils per cent.	Dosage and remarks.
May 22, 1930	45 (S)	4.12	5,000	....	...	55.5	36.5	5	1.5	1.5	Iron and ammonium citrate 3 gm. daily.
June 26, 1930	55 (T)	4.5	5,500	....	...	...	...	...	...	...	Liver, ½ pound daily plus iron.
July 31, 1930	55 (T)	4.34	...	....	...	63	36	1			
September 17, 1930	58 (S)	...	...	....	...	...	...	...	...	...	Meat juices, etc.; discontinue liver.
September 24, 1930	68 (S)	4.74	...	I 520,000	0.4	69	24	7	...	...	Meat juices; discontinue iron.
September 30, 1930	75 (S)	4.76	7,400	D 218,000							
October 14, 1930	...	4.66									
October 28, 1930	72 (S)	4.24									
November 12, 1930	72 (S)	4.35	10,000	I 810,000	0.6						

TABLE 5.—CASE 5. KATHERINE N.

Date.	Hemoglobin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Reticulocytes, per cent.	Neutrophils per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Dosage and remarks.
August 30, 1930	45 (S)	3.85	5600	...	58	30	9	1	
September 3, 1930	...	...	...	...	...	...	...	...	Iron and ammonium citrate, 3 gm. daily.
September 8, 1930	48 (S)	...	...	...	...	...	...	...	Iron, 2 gm. daily.
September 15, 1930	56 (S)	4.30							
September 23, 1930	56 (S)	5.10							
November 4, 1930	60 (S)	4.80							
December 16, 1930	68 (S)	5.10	...	...	...	...	...	...	Iron, 1 gm. daily.
February 17, 1931	96 (S)	6.20	...	...	72	14	10	4	

was negative. Hemoglobin was 45 per cent (S); red blood cell count, 4,120,000 per cu. mm.; white blood cell count, 5000 per cu. mm. Blood smear showed marked achromia of the red blood cells with moderate change in size and shape; microcytes were common; there was no polychromatophilia. Differential count of the white blood cells showed a relative lymphocytosis. The rest of the laboratory data are given in the chart.

On May 22, 1930, treatment with iron and ammonium citrate 3 gm. daily was begun. On May 29, 4 cc. of dilute hydrochloric acid was given before meals. On June 26, in addition to the above medications, she was given (by another physician) ½ pound of liver daily. She improved definitely, though slightly, on iron medication, but there was no response to added liver.

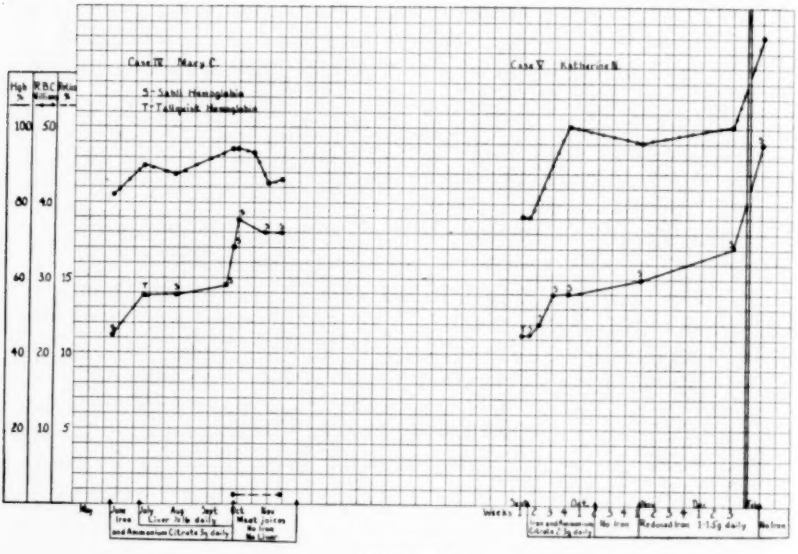


CHART IV.

On August 5, 1930, she developed suddenly a spell of numbness involving the right side of the entire body including the face; this may have been hysterical in nature as it appeared following a slight emotional upset.

On September 17, because of the history of lack of meat for 10 years, meat juices, purée of meat, scraped beef, and meat soup were started, the patient being requested to discontinue liver, iron, and hydrochloric acid. Through a misunderstanding, she continued on iron until September 24. There was marked improvement following inauguration of meat juices, even when iron was discontinued. However, this was not well sustained, so that on October 28 there was evidence of slight relapse.

Summary of Case 4. A Scotch-American housewife, aged 37 years, complained of backache, weakness, and paresthesiæ of the fingers, especially during the past year. She had not eaten meat for 10 years. Examination disclosed an atrophied tongue, pallor, and diminished vibratory sensation over the left leg. Gastric analysis

showed a faint trace of free hydrochloric acid after test meal. The blood showed a moderate degree of hypochromic anemia. Treatment with moderate doses of iron resulted in definite, though slight improvement; there was no improvement with liver; but on meat juices, etc., there was prompt increase in hemoglobin and red blood cell count. It was felt that this was a case of primary hypochromic anemia, a variant of the ordinary hyperchromic, macrocytic "pernicious" anemia.

CASE 5.—K. N., an American housewife, aged 37 years, was referred to the writer on August 30, 1930, by Dr. Maurice Evans of Boston, Massachusetts, for diagnosis and treatment. Family, marital, and past history were not significant. She complained of frequent head colds which were often accompanied by general aches and pains, sore throat, and slight fever, and persistent cough. She was nervous and easily upset. She felt constantly weak, tired, and without ambition. About a year previously she began to grow pale; shortly thereafter the tongue became itchy and very sore to acid fruits, etc. She had no gastric distress and there were no paresthesias of the extremities. She had always eaten a well-balanced diet with plenty of fruit, green vegetables, and meat; lately there had been marked loss of appetite, with some diminution in food intake. She had lost 10 pounds in weight in the past year.

Examination revealed a well-developed, rather thin woman, definitely pale. The pallor was "white" with no trace of jaundice to the skin or sclerae. The tongue was extremely smooth and glistening, with no visible papillae. There was no splenic or hepatic enlargement, and no masses were felt. Lymph nodes were not enlarged. Reflexes were hyperactive; there was no loss in vibratory sense. Blood pressure was 110 systolic and 60 diastolic. Urine was normal; stools showed no occult blood; Roentgen ray of the chest was negative. Gastric analysis showed no free hydrochloric acid 1 hour after the injection of 0.4 mg. of histamin subcutaneously. Blood Wassermann reaction was negative. Blood studies showed: hemoglobin, 45 per cent (T); red blood cell count, 3,850,000 per cu. mm.; white blood cell count, 5600 per cu. mm.; polymorphonuclear cells, 58 per cent; lymphocytes, 30 per cent; monocytes, 9 per cent; eosinophils, 1 per cent. There was moderate to marked hypochromia of the red blood cells with moderate change in size and shape and no polychromatophilia. The blood findings 4 days later were practically identical. On this day (September 3) she was started on iron and ammonium citrate, 2 gm. 3 times daily (but took doses of only 1 gm.). She was also requested to eat more food, particularly milk, between meals. On September 8, the tongue had practically ceased troubling her; she had gained 2 pounds in weight and hemoglobin had risen slightly to 48 per cent (S). She was asked to take 8 gm. of the iron and ammonium citrate daily, but this upset her so that she vomited and took the iron infrequently (about 2 gm. daily). On September 15, hemoglobin had risen to 56 per cent (S), and red blood cell count to 4,300,000 per cu. mm. She continued on 2 gm. of iron daily. On September 23, hemoglobin was 56 per cent (S) and red blood cell count 5,100,000 per cu. mm. On October 6, tonsillectomy was performed by Dr. Evans. She discontinued iron at this time. On November 4, hemoglobin was 60 per cent (S) and red blood cell count was 4,800,000 per cu. mm. She was advised to continue with 1½ gm. of iron daily. On December 16, hemoglobin was 68 per cent (S) and red blood cell count 5,100,000 per cu. mm. She felt entirely well. She continued to take 1 gm. of iron daily and on February 17, 1931, she showed the surprising figures of hemoglobin 96 per cent (S) and red blood cell count 6,200,000 per cu. mm.

Summary of Case 5. An American housewife, aged 37 years, complained of frequent cold, cough, weakness, pallor, and burning tongue. Examination disclosed marked white pallor; smooth atrophied tongue, large red tonsils. Gastric analysis disclosed no free hydrochloric acid after histamin was given. Blood showed a moderate hypochromic anemia which responded rather slowly, principally, it was felt, because the patient could not take the full dosage of iron as prescribed. There was definite rise, however, in hemoglobin and red blood cell count with disappearance of sore tongue, weakness, and fatigue. It was felt that this was another instance of a primary anemia of the hypochromic type.

Case 6.—B. I. H., No. 9751. Rose O. M., a housewife, aged 28 years, of French-Canadian parentage, was referred to the writer for study by Dr. Reuben Guralnick of Boston. She entered the hospital at 4 A.M. of February 4, 1931, disoriented and irrational, with the story of having had a convulsion ½ hour previously. Family history obtained at a later date revealed that her father had "always" been pale and had died of "cancer" at 65 years of age. An aunt of hers (her father's sister), although otherwise well, had been noticeably pale for a great many years. The patient herself had been pale since childhood; this was common knowledge to herself and her family but nothing had been done about it since she had always been able to be up and about and do her work. There had been no periods of extreme pallor or weakness until the present. Appetite had always been excellent and there had never been burning of the tongue. In September, 1930, she was delivered of a healthy infant. Both the pregnancy and puerperium were entirely normal, only a small amount of blood being lost at the time of delivery. She was entirely well for the ensuing 4 months but suddenly 3 weeks before admission she became irrational—and fainted. For 3 days thereafter she felt unusually sleepy and extremely weak. On the day before admission she suddenly became "delirious" and appeared to be deaf. At 3.30 on the morning of admission she awoke from sleep trembling violently and completely irrational. She was immediately brought to the Beth Israel Hospital. Physical examination revealed a very pale woman, almost completely disoriented. She responded rationally to simple questions and commands; response, however, was slow and she appeared very drowsy. There was a questionable Kernig sign bilaterally, but no rigidity of the neck. The tongue was smooth at the edges, otherwise normal. The rest of the examination was entirely negative except for general hyperactivity of the reflexes. Lumbar puncture was done, a clear, colorless fluid containing 2 cells per cu. mm. being obtained. Disorientation rapidly cleared, so that by 2 P.M. of the day of admission, she was entirely rational and was able to enter into an extended discussion of her history. In searching for an emotional cause for the probable hysteria, it was found that since her delivery she had had no sexual relationship with her husband who was always "tired." It was intimated that this might be a factor for hidden concern.

Although encephalitis lethargica, tuberculous meningitis, syphilis of the central nervous system and postpuerperal psychosis were considered, these could finally be ruled out and the diagnosis of hysteria made. A study of her obvious anemia was now made. She was found to have a "secondary" type of anemia: hemoglobin, 48 per cent; erythrocytes, 3,810,000 per cu. mm. The red blood cells showed moderate achromia and marked change in size and shape. No cause for this anemia could be found: vaginal and rectal examinations being entirely negative. Urine was normal; several stools

Table 6.—Case 6. Rose M.

TABLE 6.—CASE 6. ROSE M.

Date.	Hemoglobin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Blood platelets, per cu.mm.	Reticulocytes, per cent.	Polymorphonuclear cells, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils per cent.	Basophils per cent.
February 4, 1931	48 (S)	3.81	7900	735,000	2.4	72.0	12.0	14.5	1.0	0.5
February 9, 1931	45 (S)	3.57	7900	632,000	1.1	60.5	23.5	9.5	6.5	
February 15, 1931	52 (S)	4.31								
February 22, 1931	60 (S)	4.87								
March 8, 1931	76 (S)	5.53	7200							

TABLE 7.—CASE 7. CATHERINE McC.

Date.	Hemoglobin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Reticulocytes, per cent.	Neutrophils, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.
September 11, 1925	75 (T)	4.19	11,500	....	62.0	30.0	4.0	4.0	
May 26, 1930	60 (T)	4.00	7,700	....	74.0	25.0	....	0.5	0.5
August 27, 1930	55 (T)	3.71	6,900	....	73.5	24.0	1.5	1.0	
September 30, 1930	50 (T)	4.21	8,500	....	75.0	20.0	4.0	0.5	0.5
December 31, 1930	45 (T)	4.06	4,650	0.4	65.0	25.0	7.0	3.0	
February 17, 1931	47 (S)	3.80	8,600	0.2	66.5	28.5	3.0	2.0	
February 20, 1931	Iron and ammonium citrate, 8 gm. daily begun.								
February 21, 1931	....	....	....	1.8					
February 23, 1931	50 (S)	4.24	4,950	4.4					
February 24, 1931	....	....	....	4.7					
February 25, 1931	....	....	....	7.3					
February 26, 1931	54 (S)	4.24	5,750	3.5					
February 27, 1931	....	....	....	1.7					
February 28, 1931	....	....	....	2.9					
March 2, 1931	55 (S)	4.10	4,800	1.6					
March 5, 1931	61 (S)	3.90	4,900						
March 9, 1931	....	....	....	1.3					
March 10, 1931	67 (S)	4.39	4,800	1.9					
March 12, 1931	68 (S)	4.38	6,700	1.7	61.0	34.5	3.5	0.5	0.5
March 16, 1931	72 (S)	4.37	4,700	0.9	63.2	30.0	5.6	0.8	0.4

showed no occult blood; blood and spinal fluid Wassermann reactions were negative. Gastric analysis showed complete absence of free hydrochloric acid both in the fasting contents and for 1 hour after the injection of 0.6 mg. of histamin in solution. Total acid varied from 20 to 36 units per 100 cc. The rest of the laboratory data are seen in Chart V. The diagnosis of primary hypochromic anemia was made. It was felt that although this may have been aggravated by her recent pregnancy, the anemia was "primary" and probably associated with gastric atrophy and an erythroblastic bone-marrow.

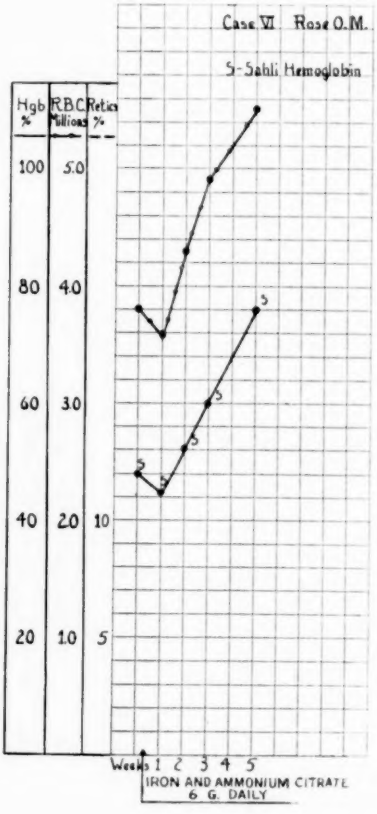


CHART V.

Clinical Course. The patient rapidly improved and was entirely free of all mental symptoms within a few hours. On February 8 she was given ferric and ammonium citrate in doses of 6 gm. daily and was discharged from the hospital on February 10 with instructions to continue with that medication and an ordinary diet without liver. On February 15, she felt much better but complained of sharp precordial pain associated with exertion. There was definite rise in hemoglobin and red blood cell count. On February 22, she showed continued improvement and was much stronger. Her appetite was ravenous and she was constantly hungry. A sample of her daily dietary was this: breakfast—grapefruit, apple sauce, 6 slices of toast

plentifully buttered, 1 egg, 2 cups of tea with sugar; morning luncheon—orange, 2 crackers; dinner—4 ounces of broiled steak, 1 potato, 2 green vegetables, 4 slices of buttered bread, jelly, 2 cups of tea; afternoon luncheon—fruit and milk; supper—4 to 5 slices of bread and butter, potatoes, cake and tea; night luncheon—fruit. Hemoglobin and red blood cell count had risen sharply, the color of the hands, face and mucosæ being noticeably improved. She was asked to continue with 6 gm. of iron daily, and there was continued rapid improvement in both hemoglobin and erythrocyte count.

Summary of Case 6. A French-Canadian woman, aged 28 years had been pale since childhood. Five months before admission she was delivered of a baby but had remained well until 3 weeks before admission when she suddenly developed some peculiar mental symptoms which were repeated on the morning of admission. The diagnosis of hysteria was made. She was found to have a moderately severe anemia of the hypochromic type associated with complete absence of free hydrochloric acid. There was prompt response to large doses of iron.

Case 7.—Catherine T. McC. (Boston State Hosp. No. 26253).* A single woman, aged 49 years, was committed to the hospital on September 2, 1925, for treatment of an "undiagnosed psychosis, (?) mental deficiency." Family history was irrelevant. At the age of 3, a questionable hydrocephalus was found. She was mentally below par, and, finally developing hallucinations and other mental symptoms, was committed to the Boston State Hospital. Physical examination was essentially negative except for slight pallor and a large head.

In May, 1930, Dr. Tryon noticed that the patient was pale. Blood studies at this time showed a "secondary" type of anemia: hemoglobin, 60 per cent (T); red blood cell count, 4,000,000 per cu.mm. No cause for the anemia could be discovered, although it was felt that it might be associated with menopausal symptoms., *i.e.*,: catamenia every 2 to 3 months, and slight menorrhagia. The dietary was the ordinary hospital one, perhaps somewhat deficient in meats, but apparently adequate, since no dietary deficiency could be demonstrated in the other patients. Pills of ferrous carbonate (1 gm. daily) were given, though not regularly, from May, 1930, until February, 1931. Despite this treatment the anemia became progressively worse as may be seen from Chart VI so that on February 18, 1931, hemoglobin was 47 per cent (S) and erythrocyte count 3,800,000 per cu.mm. Gastric analysis, done by Dr. Raskind, disclosed complete absence of free hydrochloric acid after histamin stimulation.

The writer was asked to see the patient on February 19. She was found to be up and about the ward, fairly alert mentally and able to answer questions rationally. She felt well and had no complaints. Physical examination showed a pale, rather obese woman with "pepper-and-salt" hair such as is seen frequently in pernicious anemia. The mucosæ and conjunctivæ were quite pale. There was no icterus. The tongue was completely smooth, being entirely devoid of papillæ, somewhat atrophied and shiny. Reflexes were somewhat exaggerated.

The urine showed traces of sugar from time to time. Stools were negative for occult blood. Icteric index was 4. Blood studies showed a hypochromic anemia, red blood cells being markedly hypochromic and varying widely in size and shape. Average red blood cell diameter was 6.48 micra, cells

* I am enabled to report this case through the courtesy of Dr. Tryon of the medical staff of the Boston State Hospital.

varying from 3.0 to 7.5 micra in size. Forty-seven per cent of the cells were 6.0 micra or less in diameter.

The diagnosis of primary hypochromic anemia was made and the patient started on ferric and ammonium citrate, 8 gm. daily, on February 20, 1931. There was a good reticulocyte response which reached its peak (7.3 per cent) 5 days after treatment was begun. Hemoglobin rose slowly, but erythrocytes lagged. Observations are still being continued on this patient.

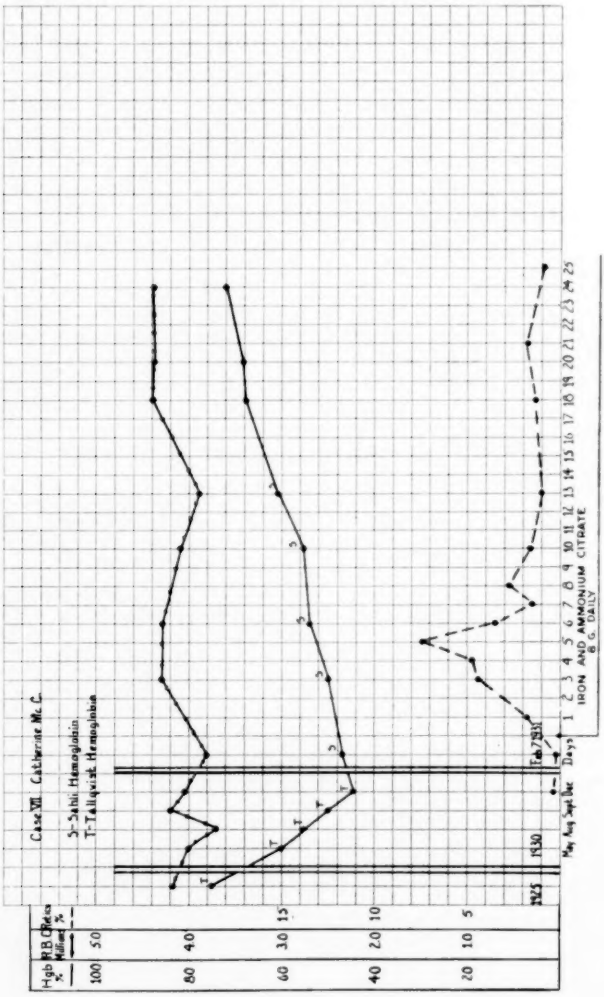


CHART VI.

Summary of Case 7. A 49-year-old inmate of a State hospital for the insane was found to have a moderate degree of hypochromic anemia without apparent cause. There was atrophied tongue and achlorhydria. Treatment with iron relieved the anemia.

TABLE 8.—ANALYSIS OF CASES.

	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.	Case 7.
Sex	Female	Male	Female.	Female	Female	Female	Female
Age	44	29	23	37	37	28	49
Nationality	Canadian-Irish	American	Russian-Jew	Scotch	American	French-Canadian	Irish-American
Symptoms:							
Weakness	+++	+++	+++	+++	++	++	0
Loss in weight	+++	+++	+	+	+	++	0
Sore tongue	+++	0	0	0	++	0	0
Anorexia	+++	+	++	+++	+++	0	0
Gastric distress	+++	0	0	+	0	0	0
Diarrhea	+	0	0	0	0	0	0
Dyspnea	+++	++	++	++	+	0	0
Paresthesias	+++	?	+	+++	0	0	0
Neurosis	0	0	0	+++	++	++	0
Other mental symptoms	0	0	0	0	0	Hysteria	Undiagnosed psychosis
Signs:							
Pallor	+++	+++	+++	+++	+++	+++	++
Icterus	0	0	0	0	0	0	0
Tongue	Atrophied	Smooth	Smooth at edges	Atrophied	Atrophied	Smooth at edges	Atrophied
Splenomegaly	?	0	0	0	0	0	0
Neurological signs	Combined system disease	0	0	"Trophic" changes of finger nails absent vibratory sense	0	Hysteria	0
Laboratora data:							
Hemoglobin	15	42	35	45	45	48	47
Red blood cells	2,000,000	3,430,000	2,100,000	4,120,000	3,850,000	3,810,000	3,800,000
Color index	0.37	0.62	0.83	0.55	0.60	0.63	0.62
Average red blood cell diameter (micra)	6.02	6.14	5.72	.....	.....	.....	6.48
White blood cells	3700	4400	3240	5000	5600	7900	8600
Platelets	267,000	100,000	56,000	.....	.....	735,000	
Free hydrochloric acid	Absent	24	1	Trace	Absent	Absent	Absent
Icteric index	4	.....	4	.....	.....	.....	4
Bone-marrow biopsy	Islands of erythro- and normoblasts	Islands of erythro- and normoblasts	Islands of erythro- and normoblasts				

Analysis of Cases. *Sex.* In the 7 cases described here, 6 were females and 1 a male; in 3 cases seen by Young at the Boston Dispensary,* all were females. All authors who have written on the subject are agreed that the disease is typically seen in women. This has naturally led to the thought that there might be a relationship to chlorosis, in fact a "latter-day" chlorosis. Sepännen,[12] on the basis of 278 adequately studied cases of hypochromic anemia of all types, finds that "simple" anemias are much more common in women than in men.

Age. Of the 7 cases studied here, 2 were in the second decade, 3 in the third decade, and 2 in the fourth. The 3 Boston Dispensary cases, ranged in age from 37 to 45. Meulengracht[13] states that these cases ordinarily occur in the fourth decade of life. This is in contradistinction to chlorosis, which, authorities agree, develops typically in girls from 14 to 20 years of age, and is rarely seen after the age of 30.

Nativity. The cases of the present series were divided as follows: 1 Canadian-Irish, 2 Americans, 1 Russian-Jew, 1 Scotch, 1 French-Canadian, and 1 Irish-American. Apparently these cases may occur in any nationality. They have been reported from Germany, Canada, the Scandinavian countries, and from this country. Brown eyes and brown hair, said to be uncommon in patients with pernicious anemia, were fully as common in the present series as blue eyes and blonde hair.

Symptoms. Ordinarily, onset of symptoms is associated with development of severe anemia with its sequelæ of dyspnea, weakness, and fatigue. Burning tongue, digestive disorders, paresthesias are common, particularly if the anemia is severe, although in Case 4 symptoms referable to the central nervous system were dominant despite the relative mildness of the anemia. The characteristic features in the symptomatology are their chronicity, and the tendency to development of relapses which are ordinarily associated with mild infections, slight bleeding, or fatigue due to increased exertion. When a definite story can be elicited, relapses are found to occur during the fall and winter, remissions during the summer. Headaches and vertigo are common. Dyspnea and palpitation are the rule. Anorexia is common; diarrhea may occur. Menstrual disorders may develop.

Physical Examination. Examination discloses pallor of varying degree, a pallor without icterus. The "greenish pallor" said to be characteristic of chlorosis was not seen in the patients of this series except possibly in Case 4 during her third relapse. The tongue is invariably smooth, shiny, frequently reddened and ordinarily without coat. It is typical of the tongue of pernicious anemia. The spleen may at times be felt, but is not usually enlarged. There may be signs of "combined system disease," such as diminished

* Personal communication to the author.

vibratory sense, diminished knee jerk, positive Babinski, etc. Changes in the finger nails ("spoon" nails, brittle nails) are common.

Laboratory Data. 1. *Gastric Analysis.* The gastric juice ordinarily shows either absent or markedly diminished hydrochloric acid. Kaznelson, Reimann, and Weiner[2] found all their cases achylic. The authors who mention this disorder, usually in passing, state that it is a simple anemia associated with achylia. It is interesting to note in this connection that chlorosis was generally associated with hyperchlorhydria. In the 7 cases reported here, 4 (Cases 1, 5, 6, 7) were completely achylic. The others showed some, though usually markedly diminished, secretion. In the 3 cases of Young's at the Boston Dispensary, all showed achylia even after subcutaneous injection of histamin. Achylia is thus usually present, but is not a constant finding.

2. *Icteric Index.* This was found to be low in those cases in which the test was performed. In Cases 1, 3 and 7, the index was 4 (normal 6 to 10). The low index is probably due to the normal amount of blood destruction in the presence of diminution in number of red blood cells.

3. *Blood Findings.* Hemoglobin is reduced to a greater degree than the red blood cell count. The color index is thus below unity and the red cells hypochromic. The lowest readings of hemoglobin and red blood cells were seen in Case 1—hemoglobin 12 per cent (S); and red blood cell count 1,800,000 per cu.mm. Besides the hypochromia, changes in size and shape of red blood cells are quite striking at times. Polychromatophilia and increase in reticulocytes are not ordinarily seen. Normoblasts may at times be seen, especially if the anemia is severe. Red blood cell diameter is much reduced, ranging in these cases from 5.8 to 6.2 micra. Leukopenia (to as low a figure as 2 to 3000 white blood cells per cu.mm.) is the rule, this being due to an absolute reduction in granulocytes. The nuclei of the polymorphonuclear cells are usually many lobed, resembling the "pernicious anemia neutrophil." The lymphocytes are increased in relative number. Monocytes are ordinarily diminished. Blood platelets are ordinarily diminished during relapse but may be greatly increased during remission. During this phase, there is a rise in reticulocytes, not to so great an extent, to be sure, as in pernicious anemia, but to fairly high levels (9 to 10 per cent). This rise usually occurs within a few days after onset of therapy, at a somewhat shorter interval than in pernicious anemia. Leukocytes may be 10,000 or 12,000 per cu.mm., the increase being due to a marked rise in polymorphonuclear cells. Blood platelets become increased to a striking degree—in 1 case rising from 40,000 to 1,250,000 per cu.mm. Once having become increased, they tend to remain at a high level.

4. *Bone-marrow Biopsy.* Biopsy of the sternal marrow was performed in 3 of the present series of cases, the technique of Seyfarth[14]

being used. Smears and sections were made. The same findings were present in all 3 cases. Despite the severe anemia, the leukopenia, the reduction in thrombocytes—all of which would lead one to suspect some degree of aplasia of the marrow—the bone marrow was crowded with nucleated red cells.* These were all of the normal erythronormoblastic type, no megaloblasts being seen. Islands of erythroblasts were common. These were composed of fairly large hemoglobin-containing nucleated cells, larger than the normoblast and containing a nucleus composed of blocks of chromatin. Kaznelson, Reimann, and Weiner[2] have described this identical picture in their biopsied cases of the disease. The overabundance of nucleated red cells, the islands of immature hemoglobin-containing cells are reminiscent of the state of the marrow in pernicious anemia, in which, despite the anemia, there is overabundance of nucleated red cells and islands of a special type of immature red cells—the megaloblast.

Treatment. One of the most characteristic features of the disease is the prompt and dramatic response to large doses of iron. It has been the experience of all who have written on this subject that the dosage of iron must be large, from 3 to 6 gm. daily. In Central Europe reduced iron has been used. In a large group of patients with hypochromic anemia of all types, the author has used with excellent results the soluble ferric and ammonium citrate in 25 per cent aqueous solution. The dosage has varied from 2 to 8 gm. daily. In these cases of primary hypochromic anemia a dosage of 3 to 6 gm. daily has been found adequate to induce a remission within 3 to 5 days. On the third or fourth day following the induction of treatment with iron, the patient may suddenly develop a sensation of strength and well-being heretofore absent, as well as a desire to eat. The appetite becomes voracious, the soreness of the tongue disappears, paresthesias, if present, diminish, and there is marked gain in weight. This is well brought out in Cases 1, 2 and 6 of this series. Coincident with the onset of these symptoms, there is a rise in reticulocytes which has been discussed above. The suddenness of onset of remission, the voracious appetite which develops, are strikingly reminiscent of the effect of liver extract in patients with pernicious anemia. As with liver in the latter disease, the dosage of iron in primary hypochromic anemia must be adequate. Thus in Case 1, there was a cessation of rise in hemoglobin red blood cell count on 3 gm. of iron daily, but with 6 gm. daily, there was again a prompt response. If the iron is discontinued, a relapse may occur (Cases 1, 2, 3). These considerations are suggestive of a deficiency in iron. It is probably advisable, therefore, when normal hemoglobin and red blood cell counts have been obtained, to main-

* It has been conclusively shown by Custer and others that the marrow of different bones will show widely different pictures in a given case. The sternal marrow is notoriously one of the last to become hypoplastic.—EDITOR'S NOTE.

tain the patient on a relatively small dose (1 gm.) of iron daily.* Table 8 presents in tabular form the symptoms, signs, and laboratory data noted in the cases presented in this paper.

Discussion. As noted in the introduction, it seems difficult, so firmly has the idea become ingrained, to conceive of a primary anemia with the so-called "secondary anemia"—hypochromic, microcytic—type of blood picture. The entire classification of the anemias is at the present writing in a state of confusion: pernicious anemia no longer has its pernicious outlook; we see no more of the "green sickness" chlorosis. It would be advisable, to be sure, to classify the anemias on purely etiologic grounds, but this ideal is as yet far from attainment. Some of the proposed classifications, each emphasizing a different angle of the problem, are as follows: (1*a*) *primary* (cause not known) and (1*b*) *secondary* (cause known); (2*a*) *essential* (in which the anemia is the dominating symptom): chlorosis, pernicious anemia, aplastic anemia; familial hemolytic jaundice and (2*b*) *secondary* (in which the anemia is a phenomenon secondary to a separate disease entity); (3*a*) *hyperchromic* (in which there is anemia and yet the red blood cell has its full complement of hemoglobin) and (3*b*) *hypochromic* (in which the red blood cell is insufficiently filled with hemoglobin); (4*a*) *macrocytic* (in which the average red cell diameter is above the normal of 7.5 to 7.8 micra) and (4*b*) *microcytic* (the average red blood cell diameter below 7 micra); (5*a*) anemias due to *faulty blood formation* (pernicious anemia, chlorosis, aplastic anemia) and (5*b*) *increased blood destruction*, etc. In spite of all these attempts to classify the anemias on purely hematologic or physiologic grounds, the old descriptive names of pernicious anemia, chlorosis, familial jaundice have persisted in current usage. Until the ideal classification based on etiology is attainable it might be advisable to classify the anemias on purely histopathologic grounds. Thus pernicious anemia would be megaloblastic anemia; the name aplastic anemia would stand; the anemia here discussed would be erythronormoblastic anemia; the anemia of familial jaundice might be reticuloendothelial or macrophagic anemia. It is true that the histopathology of the bone marrow has not as yet been sufficiently studied to permit any clear-cut descriptions of all the anemias, but with the increasing use of the bone-marrow biopsy as a diagnostic procedure, this might be possible. It is to be remembered in this connection that such an admittedly temporary descriptive classification is widely used for tumors where again the etiology is unknown.

The megaloblastic (hyperchromic, macrocytic) anemia called "pernicious" has been shown by the researches of Castle[8] to be a virtual deficiency disease due to inadequate protein digestion in a peculiarly diseased stomach. However, the cause for the gastric

* Since writing this paper, further data on the effects of various substances on the anemia have been obtained. It is planned to incorporate these data in another article.

atrophy has not as yet been found; nor has it been determined why these individuals develop an embryonic megaloblastic reaction rather than the ordinary erythronormoblastic response; again the cause of spontaneous remissions has not been elucidated. The megaloblastic marrow has brought up the idea of a constitutional factor—well borne out in certain pernicious anemia families. At any rate there is now no question that gastric digestion in pernicious anemia is at fault. This is seen to be due to gastric atrophy which in turn may be occasioned by unknown factors or may be congenital, syphilitic, infectious, or the result of pregnancy.[15] Various authors have concluded that pernicious anemia is a symptom complex due to diverse causes associated with a constitutional factor: a megaloblastic bone-marrow. This highly unusual marrow is, in the final analysis the only pathognomonic sign of the disease—the symptomatology of jaundice, macrocytosis, hyperchromia, smooth tongue, nervous system signs, gastric anacidity, even response to liver therapy being possible in other conditions. It may well be, therefore, that (1) given an embryonic rest of megaloblasts in the bone marrow, an individual with (2) gastric atrophy may, with (3) a stimulus, such as infection, pregnancy or fish tapeworm, develop the anemia ordinarily spoken of as pernicious. It is possible, however, that every individual (regardless of embryonic rests or constitutional types) who has the type of gastric atrophy found in pernicious anemia will in the course of time develop the peculiar bone-marrow picture which is found in pernicious anemia. This concept is certainly difficult of proof.

The group of cases presented in this paper parallels very closely a group of cases of pernicious anemia; at times the resemblance is indeed striking. Thus in Case 1 we see a history of remissions and relapses, sore tongue, paresthesias, diarrhea, a smooth tongue, absence of hydrochloric acid after histamin, neurologic signs, leukopenia, thrombocytopenia—in fact all the symptoms and signs of pernicious anemia except the hyperchromia, the macrocytosis, and the elevated icteric index. In the final analysis, the only difference between the 2 types of cases is that in pernicious anemia the marrow is crowded with megaloblasts which, if not embryonic, are certainly not normal; whereas in the other type, one sees an erythronormoblastosis: a crowding of the marrow with smaller, more normal cells. In both types there appears to be a defect in maturation, for despite the marked hyperplasia of nucleated red cells there is in both instances a marked anemia. The defect in maturation in the first type has been shown by Castle[8] to be due to a virtual deficiency in a certain protein subsequent to impaired gastric digestion. Most of the cases presented here are deficient in free hydrochloric acid which hints at some gastric disturbance. The accompanying glossitis is also evidence in this direction. The defective gastric digestion may lead to an inadequate digestion of organic

iron, thus permitting (to paraphrase Castle[8]) the development of a virtual deficiency in the presence of a diet adequate for the normal individual. This defective maturation of red cells may be remedied in the first instance by sufficient dosage of liver extract, properly digested protein or gastric extract; and in the second instance by inorganic iron in sufficient dosage. Whether disturbed protein digestion alone brings about a megaloblastosis or whether an embryonic rest of megaloblasts is also necessary is not yet clear. In this connection, one may speculate that an individual with a megaloblastic marrow will develop under certain conditions the ordinary pernicious anemia, whereas one with a normal marrow will under the same conditions develop the type of anemia presented here.

Apropos of this, the interesting observation has been made by Faber and Gram[6] of a family in which there were 3 patients with achylia gastrica; 2 of them, father and son, died of pernicious anemia, the third, a daughter showed a pronounced "relapsing microcytic type of anemia." The latter patient ("curiously enough," the authors note) showed a typical glossitis.

More extended observations on this unusual family have recently been made by Gram.[16] He has been able to study 3 generations. The father and his 2 eldest sons died of typical pernicious anemia. A daughter, aged 43, in 1919 had achylia gastrica, glossitis, and a microcytic anemia relieved by iron. In 1928, she had a "latent" pernicious anemia blood picture, and in 1929 full-blown pernicious anemia. Another daughter of 47 also had a pronounced microcytic anemia associated with achylia and responding to iron. Of 10 grandchildren, most had marked hyperacidity and gastric hypersection, interpreted as possible gastritis. Gram felt, on the basis of these observations, that pernicious anemia was dependent on an hereditary factor and that it might pass through these phases: acid gastritis, slight temporary "simple" anemia, dyspepsia, glossitis, achylia, severe temporary "simple" anemia, and finally pernicious anemia. Other authors have noted the occurrence of a "simple" anemia in members of a family in which pernicious anemia is present.

Faber[6] in 1913 first pointed out that an anemia of some type was found in 28.5 per cent of 207 patients with achylia. In 1924, the same author[6] found anemia (usually hypochromic or "simple") in 41 per cent of all cases with achylia. Kaznelson, Reimann, and Weiner[2] also have observed 25 cases identical with the ones described here; they discuss gastric achylia as an etiologic factor.

McLester,[17] in a recent article on "Clinical Syndromes that Include Achlorhydria," reports a few cases with the typical symptomatology of pernicious anemia, sore tongue, and achlorhydria. His Cases 1, 2, 3, and 7 resemble the ones described here. In Case 2, McLester makes the interesting observation that he is "inclined, in spite of failure to find typical blood changes, to regard her disease as pernicious anemia." He states that the "difficulty of categorically

labeling these patients illustrates the possible kinship between the diseases of this group." Christian,[18] in an article on "The Achlorhydria Family Tree of Diseases" made somewhat similar observations.

The reasoning, which takes into account "embryonic rests," etc.,[19] is speculative, and somewhat impaired by the experiments of Castle.[8] In one of these, protein incubated with the gastric juice of 2 cases of "chronic chlorosis" was active in causing a remission in pernicious anemia. The reverse was apparently not tried. Further experimentation on these points is advisable. The observations in Gram's[16] family of pernicious anemia, particularly on the patient who passed through the stages of microcytic anemia, latent pernicious anemia, and full-blown pernicious anemia, are interesting in this connection. I have recently observed at the Beth Israel Hospital another instance of this transition from a hypochromic anemia responding to iron to a hyperchromic anemia typically "pernicious" responding to liver. From the above speculations and with the cases presented here in mind, the possibility presents itself that "pernicious" anemia may be of 2 types: the ordinary megaloblastic (macrocytic, hyperchromic) and the unusual (or but little known) erythroblastic (microcytic, hypochromic) anemia.

What relationship has primary anemia of the erythroblastic, hypochromic type to another disease called chlorosis? This disease, a primary or essential anemia occurring in women and characterized by an extremely low color index, is universally considered to be at the present time almost defunct. One of the mysteries of medicine is how a disease so common in 1880 and 1890, should in 1930 have become so rare that one never sees an example of it. It is possible, to be sure, that the diagnosis of chlorosis was being made so commonly during the last century, that any girl or young woman who was slightly pale and who complained of fatigue, weakness, vertigo, and menstrual disturbances was considered to be chlorotic. At the present time, the tendency may be to call these cases "neurosis" and the accompanying anemia (always of the hypochromic type) "secondary." Can it be that the cases described here are not really instances of a "new" type of idiopathic anemia, but rather examples of chlorosis? Mills,[4] in discussing "idiopathic hypochromic anemias" speaks of "present-day chlorosis," in which the hemoglobin is reduced, although the red blood cell count is normal, as are the counts of the white blood cells and blood platelets. He says that free hydrochloric acid is not infrequently absent from the gastric juice and that response to Blaud's pills is rare; he recommends highly ultra-violet ray therapy. Schulten[3] also speaks of this latter-day chlorosis ("spät-chlorose") which responds to large doses of iron. In discussing the relationship between gastric achylia and "simple" anemia, Faber and Gram[6] state that although this anemia may resemble chlorosis, it differs from it by its presence in

both sexes and by its tendency to recur. Kaznelson, Reimann, and Weiner[2] call the disease "achylic chloranemia" (achylische chloranämie). According to various treatises on chlorosis,[21] the disease is characterized by very slight, if any reduction in red blood cells and by a hyperchlorhydria in the large majority of instances. It usually develops at puberty, may recur up to the age of 30, but tends to disappear before that age, especially if marriage or pregnancy (or both) have supervened. It is said never to begin after the age of 27. Sore tongue and symptoms of combined system disease are never mentioned.

Let us examine critically the case presented here with regard to chlorosis.

Case 1. A married woman, aged 44 years, disease of five years' duration; hemoglobin, 12 per cent; red blood cell count, 1,900,000 per cu. mm.; white blood cell count, 3200 per cu.mm.; achlorhydria; central nervous system manifestations. All of these manifestations, the age group, the severity of the anemia appear to rule out chlorosis.

Case 2. A man, aged 37 years. The sex alone rules out the disease, although certain authors report cases of chlorosis occurring in men. This is held to be impossible by most authorities. The age is wrong for chlorosis.

Case 3. The marked anemia associated with leukopenia and thrombocytopenia, the low gastric acidity, all appear to rule out the disease. It is possible, however, that this case might have been called chlorosis in the last century.

Case 4. The age, sore tongue, almost complete absence of free hydrochloric acid from the stomach, the neurologic symptoms would rule out chlorosis according to the authorities consulted.

Case 5. The age, sore tongue, absence of free hydrochloric acid from the stomach here again tend to rule out chlorosis.

Case 6. The peculiar symptomatology, the absence of free hydrochloric acid from the stomach appear to rule out chlorosis.

Case 7. The age, the gastric anacidity again appear to rule out chlorosis.

To summarize, the last 4 cases, being relatively mild, suggest chlorosis but are probably ruled out by the age groups, the lingual manifestations, the tendency to diminution or absence of free hydrochloric acid, and central nervous system symptoms. The first 3 cases are too severe to be classed as chlorosis. After all, when we discuss chlorosis, we are speaking of what is to us of the present medical generation an indefinite disease with a peculiar name and an unknown pathology. Until we know more of the pathology and pathologic physiology of that disease, it seems wise at present to drop the term chlorosis. If the instances of so-called chlorosis are intensively studied with present-day methods, it is possible that they will all be placed in the group under discussion here.

The cases described here, then, present a symptomatology which is strikingly like that of pernicious anemia. The objective phenomena of pallor, smooth tongue, central nervous system manifestations, and achlorhydria resemble pernicious anemia; the blood findings of achromia and microcytosis at first glance seem to rule out pernicious anemia, but when one considers that the marrow in both cases is hyperplastic—in pernicious anemia megaloblastic, in these cases erythronormoblastic—and the immature nucleated red cells ready to maturate if given the proper stimulus, the blood picture becomes rather subsidiary to a broader conception of the disease. There is possible relationship of this group of cases to chlorosis, but in view of such factors as age group, sore tongue, achlorhydria, etc., this relationship seems to be minimized.

Summary and Conclusions. Seven cases of an anemia are described in which, although the symptomatology was that of pernicious anemia, the hematologic findings were those of a "secondary" anemia. Most of these cases gave a history of remissions and relapses of anemia, sore tongue, gastro-intestinal symptoms, and parasthesias. Objectively, they showed pallor without icterus, atrophied tongue, "spoon" nails and, at times, signs of "combined system disease." All known causes for a secondary anemia were absent. Achlorhydria or hypochlorhydria was present. The blood picture showed low color index, hypochromia, low average red blood cell diameter, leukopenia, relative lymphocytosis and thrombocytopenia. Sternal bone-marrow biopsies in 3 cases disclosed, despite the severe anemia, marked hyperplasia due to crowding with erythroblasts and normoblasts. The anemia and all of the symptoms responded promptly to large doses of inorganic iron, but there was a tendency to relapse when iron was discontinued.

The relationship of this anemia to the megaloblastic hyperchromic anemia called "pernicious" is discussed in detail. Pernicious anemia shows pathologically a hyperplastic marrow crowded with abnormal or embryonic nucleated red cells called megaloblasts which apparently maturate very inefficiently unless liver or stomach or normally digested protein is given. The erythroblastic hypochromic anemia described here shows pathologically a hyperplastic (sternal) marrow crowded with the more normal erythro- and normoblasts which apparently maturate very inefficiently unless inorganic iron is given in large doses. This anemia may be due to a virtual deficiency subsequent to inadequate digestion of organic iron.

The possibility that the cases described here are instances of chlorosis is discussed and rejected.

It is felt (1) that the hypochromic anemia described here is "primary" or "essential;" (2) that it is related to pernicious anemia of which it may be an unusual type; (3) that it is probably dependent upon an inadequate gastric digestion of organic iron which may

thus lead to faulty hemoglobin synthesis and improper maturation of erythro- and normoblasts in the bone marrow.

NOTE.—Since this paper was written 5 other cases closely similar to those cited have been observed.

BIBLIOGRAPHY.

1. Schilling, V.: The Blood Picture, Am. ed., St. Louis, The C. V. Mosby Company, 1930.

2. Kaznelson, P., Reimann, F., and Weiner, W.: Achylische Chloranämie, Klin. Wchnschr., 1929, **8**, 1071.

3. Schulten, H.: Zur Behandlung hypochromer Anämien mit maximalen Eisendosen, Münch. med. Wchnschr., 1930, **77**, 355.

4. Mills, E. S.: Observations on the Diagnosis and Treatment of Primary Anemias, Canadian Med. Assn. J., 1930, **22**, 666.

5. Altschuler, G.: Sur le pathogénie de l'anémie hypochrome chronique, dite achylique, Acta med. Scand., 1929, **70**, 119.

6. Faber, K.: Anämische Zustände bei der chronischen Achylia gastrica, Berlin. klin. Wchnschr., 1913, **50**, 958. Faber, K., and Gram, H. C.: Relations Between Gastric Achylia and Simple Pernicious Anemia, Arch. Int. Med., 1924, **34**, 658. Faber, K., and Gram, H. C.: The Association of Achlorhydria and Anemia of Different Types in Three Members of the Same Family and the Behavior of the Color Index in Pernicious Anemia, Arch. Int. Med., 1924, **34**, 827.

7. Wahlberg, J.: Liver Diet and Reticulocyte Reaction in Simple Anemia, Acta med. Scand., 1929, **34**, 104, suppl.; Acta med. Scand., 1929, **72**, 143.

8. Castle, W. B., Townsend, W. C., and Heath, C. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia III, AM. J. MED. SCI., 1930, **180**, 305.

9. Mettier, S. R., Minot, G. R., and Townsend, W. C.: Scurvy in Adults, J. Am. Med. Assn., 1930, **95**, 1089.

10. Witts, L. J.: Achlorhydria and Anemia, Practitioner, 1930, **124**, 348.

11. Waugh, T. R.: Hypochromic Anemia with Achlorhydria, Arch. Int. Med., 1931, **47**, 71.

12. Sepännen, Anni: Zur Frage der Pathogenese der hypochromen Anämie, Acta med. Scand., 1929, **34**, 62, suppl.

13. Meulengracht, E.: Pernicious Anemia and Liver Treatment, Acta med. Scand., 1929, **34**, 62, suppl.

14. Seyfarth, C.: Die Sternumtrepanation, eine einfache Method zur diagnostischen Entnahme von Knochenmark bei Lebenden, Deutsch. med. Wchnschr., 1923, **49**, 180.

15. Fontana, A., and Lageder, K.: Ueber einige Formen pernizioser Anämie mit bekannter Atiologie, Virchow's Arch. f. path. Anat., 1929, **273**, 553.

16. Gram, H. C.: Further Observations on a Family Showing Many Cases of Pernicious Anemia, Acta med. Scand., 1929, **34**, 107, suppl.

17. McLester, J. C.: Clinical Syndromes That Include Achlorhydria, J. Am. Med. Assn., 1930, **95**, 719.

18. Christian, H. C.: The Achlorhydria Family-Tree of Diseases, Northwest Med., 1925, **24**, 531.

19. Piney, A.: Recent Advances in Hematology, Philadelphia, P. Blakiston's Son & Co., 1927.

20. Von Noorden, K.: Chlorosis in Diseases of the Blood, Nothnagel's Encyclopedia of Practical Medicine, Am. ed., Philadelphia, W. B. Saunders Company, 1905, p. 339. Immerman, H.: Chlorose in von Ziemssen's Handbuch der speziellen Pathol. u. Therapie, 1879, Bd. **13**, 2 Halfte, p. 275, 2 Aufl., **Leipzig, F. C. W. Vogel.** Rosenbach, O.: Die Entstehung und hygienische Behandlung der Bleichsucht, Leipzig, 1893. Hayem, G.: Du sang et de ses alterations anatomiques, 1889, Paris, G. Masson, p. 614.

IDIOPATHIC HYPOCHROMEMIA.

By Edward S. Mills, M.D., M.Sc.,

DEMONSTRATOR IN MEDICINE, MC GILL UNIVERSITY; ASSISTANT IN MEDICINE, MONTREAL GENERAL HOSPITAL, MONTREAL, CANADA.

In a preliminary paper[1] published in February, 1930, the author reported a series of 10 cases of anemia, all in women, and characterized by a chronic prolonged course, a "secondary" type of blood picture, a tendency to resist ordinary anemia therapy, and almost invariably by the absence of free hydrochloric acid from the gastric contents. It was further shown that these cases, unusually resistant to ordinary therapy, could be greatly benefited by adding small amounts of copper salt to Blaud's mass. The term idiopathic hypochromic anemia was suggested for this disease.

The conviction that such cases represented a disease entity separate and distinct from chlorosis and postpartum anemia (Osler[16]), with which the condition has certain features in common, appears to have originated simultaneously in this country[2] and in Germany.[3] Isolated instances of "secondary" anemia of undetermined etiology have been reported for many years. Faber's paper[4] in 1913 contains the first clear-cut description of the disease. Since this time similar cases have been reported by Weiner and Kaznelson[5] (1926), Spenson[6] (1926) and Altschuller[7] (1929) and others. Although brief reference to simple anemia with achylia was made by Lee and Minot[8] in 1928, the first adequate descriptions of the disease appeared the following year.[2,3]

Nomenclature. At the present time there appears to be no unanimity of opinion as to the most suitable nomenclature for the disease. Weiner and Kaznelson,[5] who probably deserve credit for attempting to establish the disease as a clinical entity, referred to the 3 cases which they published in 1926 as "cryptogenic achylic chloranemia." In their later and larger series of cases[3] they employ the term achylic chloranemia. Watkins[2] uses the rather paradoxical title "idiopathic secondary anemia." Mills suggested the term idiopathic hypochromic anemia to overcome the word "secondary," which refers only to the type of blood picture. The use of hypochromic to describe these cases has been accepted independently by Schulten[9] and by Waugh.[10] More recently Mettier and Minot[11] (1931) have referred to such cases as chronic chlorosis, though this term would appear to be inappropriate as the disease differs from chlorosis in that hyperchlorhydria, not achlorhydria, is a feature of the latter.

In our opinion the choice of a name for the disease lies between achylic chloranemia and idiopathic hypochromic anemia or hypochromemia. The latter is preferred because occasionally a case is

encountered with a small amount of free hydrochloric acid in the gastric contents and which cannot be otherwise distinguished from typical instances of the disease. Witts'[12] suggestion "simple achlorhydric anemia" is open to the same criticism.

Incidence of the Disease. An accurate determination of the incidence of idiopathic hypochromemia is not easily obtained in a medical outpatient clinic where cases are not classified according to disease. In 1929 10 cases were recognized in the medical outpatient department of the Montreal General Hospital, and in 1930 10 new cases out of a total of 6863 medical admissions, though the true incidence of the disease is probably much greater. Nevertheless, Witts was able to collect only 50 cases at Guy's Hospital by analyzing the records from 1922 to 1929. Seppänen[13] has recently invesigated 209 cases of hypochromic anemia. Fifty-five were due to hemorrhage, 61 to infections, 33 to malignant tumors and 19, or 10 per cent, were of the idiopathic type. It is of interest that all the idiopathic cases were females whereas the other types were evenly divided between the sexes.

Predisposing Factors. (*a*) *Age and Sex.* All of our cases have been women despite a diligent search for instances of the disease among the male sex. Only one instance of the disease in the male has been recorded in the literature.[12] The disease shows a marked predilection for the fourth decade. Fifteen of 23 cases, or 65 per cent, occurred between the two ages of 30 and 40 years, usually toward the end of this age period. The youngest case was a girl aged 26 and the eldest a woman aged 61 years.

(*b*) *Occupation.* Overwork, poor hygienic conditions and improper food appear to play a minor rôle in the etiology. A lot has been written about nutritional anemia and the militating influence of overwork and unhealthy surroundings upon anemia. No doubt such circumstances are important, but they are not intimately concerned in the pathogenesis. Four of the cases in this series lived in ideal surroundings and had an abundant and well-balanced diet. In but one instance could dietary influences be blamed for the anemia and in this case the response to iron and copper therapy was rapid and complete in spite of the same home conditions.

(*c*) *The Influence of Pregnancy.* At first sight pregnancy would seem to play an important rôle in the pathogenesis of the disease. Three cases gave a history of a number of pregnancies rapidly succeeding each other with the development of anemia during 1 or more of these, and 5 others first noticed symptoms following labor or miscarriage. A brief résumé of 2 of the cases will serve to illustrate what is true of all cases, namely, that the pregnancy is a complication rather than an etiologic factor in the disease.

Case 1. Mrs. L., 7833–29, aged 38 years, is the mother of 3 children. She first became anemic following the birth of her second child, now 12 years of age, and at that time was treated with partial success. Ever since

this time she has been pale and has had fatigue and dyspnea on mild exertion. Toward the end of 1928 she became worse, having syncopal attacks and paresthesia of the fingers and toes. In June, 1929, when her hemoglobin was 60 per cent, she was placed on a mixture of iron and copper. In September, 1930, the hemoglobin was 84 per cent. She returned in October, pregnant and since this time her symptoms have gradually returned. On December 24 the hemoglobin was only 55 per cent.

Case 2. The second case is a young woman aged thirty-two years, the wife of a dentist, who has been married 8 years and has been sterile. She had "always been pale and anemic" and had been treated with various iron preparations for some years. She took liver and liver extract for 3 months without improvement. Under iron-copper therapy the hemoglobin rose from 40 per cent to 80 per cent with disappearance of her symptoms and waxy color. A year later she became pregnant, following which her pallor temporarily reappeared.

Obviously pregnancy is not the cause of the anemia in these cases, but the added burden which reduces the hemoglobin level to a point incompatible with the pursuit of the ordinary duties of life. Other cases have shown similar relapses after focal infection.

(*d*) *Heredity.* Only 1 case of the series gave a family history of anemia, but 1 woman brought her daughter, aged 14 years, to the clinic where the child was found to be decidedly chlorotic.

Achlorhydria. An important factor common to all cases was the marked reduction or complete absence of free hydrochloric acid from the gastric contents after the Ewald test breakfast. In this series of 23 cases, 19 had achlorhydria, 2 had low free hydrochloric acid at one period during the fractional meal and 2 were not tested. The response to histamin was not tried. The subsequent course in the 2 untested cases and their response to treatment seems to justify their inclusion in this group. In Witts' series,[12] 44 cases had achlorhydria while 6 cases had some free hydrochloric acid in one fraction.

For a long time achlorhydria has been suspected to be intimately associated with the underlying cause or causes of idiopathic types of anemia. Faber and Gram's[14] careful study on a series of 90 cases of achylia showed 41 per cent to be anemic, the majority of the "secondary" type. It may, therefore, be taken as proved that achlorhydria or achylia predisposes to the production of anemia of the idiopathic type, though this defect is not the cause of the disease. Mettier and Minot's[11] recent observations indicate that the response of anemias characterized chiefly by hemoglobin deficiency to iron therapy is much enhanced when the iron is given in an acid medium. They suggest that achylia results in a change in the hydrogen-ion concentration of the intestinal contents unfavorable to the absorption of iron. It would seem, however, that the acidity or, rather, the alkalinity of the intestinal contents, where iron is actually absorbed, would not be greatly influenced by the degree of acidity of the stomach contents, since neutralization is rapidly effected in the duodenum. Whatever may be the secretory defects associated with achylia it seems certain that the individual with a deficiency

TABLE 1.—ANALYSIS OF CASES.

Case No.	Name.	Age.	Nationality.	Duration of anemia.	Pregnancies.	Paresthesia.	Cord changes.	Spleen.	Glossitis.	Gastric contents.	Blood picture.									Complications.	Results of treatment.
											R. B. C.	W. B. C.	Hb.	Van den Bergh.	Platelets.	R. B. C., diam.	Polys.	Lymphs.	Eosins.	Monos.	
1	N. E. (601–29)	40	Irish	"Always"	0	0	0	P	0	0/18	3.6	5,200	30	0	257,000	7.3	55	45	..	..	Infected finger	Good
2	J. C. (2351–30)	36	Can.	1 year	0	P	0	0	0	0/?	3.9	3,000	49	0	409,000	7.6	60	34	6	3	Myxedema	Good
3	O. J. (18155–25)	31	Can.	5 years	5	P	0	0	0	0/?	4.3	7,200	55	0	....	7.8	70	26	1	..	None	Good
4	F. M. (10545–29)	36	Can.	1 year	0	P	0	0	0	0/12	4.5	6,000	50	0	....	7.6	70	30	..	..	None	Good
5	E. M. (3247–26)	41	Eng.	2 years	0	P	0	0	0	0/11	3.7	9,150	70	0	....	7.9	79	17	1	..	None	Good
6	P. L. (4042–27)	39	Scot.	½ year	0	P	0	0	0	0/14	3.7	4,950	38	0	335,000	..	66	33	1	..	Chr. ulcer. colitis	Fair
7	C. M. (5755–29)	58	Scot.	7 years	0	0	0	0	0	0/12	4.3	3,700	48	0	....	7.3	61	32	3	2	None	Good
8	H. F. (4202–29)	26	Can.	10 years	0	0	0	0	0	0/10	3.0	3,300	42	0	375,000	7.0	64	33	..	3	None	Good
9	R. S. (6737–30)	40	Scot.	4 years	0	0	0	0	0	0/7	4.5	8,700	41	0	205,000	7.2	63	33	..	4	Chronic cholecystitis	Good
10	R. C. (14256–29)	39	Scot.	1 year	2	0	0	0	0	0/27	3.9	5,800	58	0	275,000	7.9	58	40	1	1	None	Good
11	J. Mc. (1864–25)	34	Scot.	5 years	0	P	0	0	0	0/0	3.1	7,500	45	0	283,000	7.8	58	40	..	2	None	Poor
12	J. W. (1095–25)	42	Eng.	7 years	1	P	0	0	0	0/15	4.6	5,500	53	0	180,000	7.7	72	22	2	2	None	Poor
13	J. H. (5227–23)	35	Can.	1½ years	5	P	0	0	0	0/35	4.3	4,400	56	0	333,000	7.7	55	43	1	1	None	Good
14	W. L. (7833–29)	38	Eng.	1 year	3	P	0	0	0	0/10	4.2	6,000	60	0	215,000	7.4	68	32	..	..	None	Poor
15	J. H. (5227–23)	35	Eng.	"Years"	0	P	0	0	0	0/35	4.3	4,450	56	0	....	7.9	55	43	1	1	None	Good
16	P. C.	45	Can.	2 years	0	0	0	0	0	?	4.0	5,400	61	0	162,000	7.3	62	36	3	..	None	Good
17	J. Y.	61	Eng.	"Years"	0	P	0	0	0	?	3.1	9,700	30	0	510,000	7.6	66	26	3	1	None	Good
18	R. A. (7182–30)	35	Eng.	2 years	6	0	0	P	0	8/45	3.9	5,400	38	0	150,000	7.4	61	39	..	..	Birth trauma	Good
19	T. W.	46	Scot.	4 years	0	0	0	0	0	0/5	4.6	8,200	47	0	....	7.6	..	..	..	..	None	Good
20	A. W. (16564–30)	32	Can.	1½ years	2	0	0	0	0	0/18	2.8	5,500	36	0	213,000	..	66	28	..	4	None	Good
21	W. M. (13846–28)	47	Eng.	"Years"	0	0	0	0	0	0/12	3.9	5,650	68	0	....	..	..	..	..	..	None	Untraced
22	O. C. (2336–26)	37	Can.	1 year	5	..	0	P	0	14/33	3.7	4,950	47	0	300,000	7.7	43	63	3	1	None	Good
23	C. G.	32	Can.	"Years"	0	0	0	0	0	0/20	3.7	5,900	40	0	255,000	7.3	52	45	1	2	None	Good

or absence of free hydrochloric acid in his gastric contents is even more likely to develop a hemoglobin deficiency anemia than he is to develop anemia of the Addisonian type. In Faber's[4] series of 207 cases of achylia gastrica, 59 patients were anemic, and of these 22 were of the Addison type while the remaining 37 were of the secondary type, a proportion of almost 1 to 2.

Symptomatology. The symptoms of the disease are essentially those of any severe form of anemia—namely weakness, lassitude and fatigue on mild exertion. The onset of this train of symptoms was invariably so insidious that the patient was unable to state just when she was last perfectly well. Many claimed to have been anemic all their lives and gave a history of frequent recourse to the family physician for iron tonics, usually without benefit. Of the 20 cases in this series 15, or 75 per cent, sought treatment for symptoms of anemia. Two came to the hospital as a result of minor accidents, and 1 case because of an acute cholecystitis, though she had been anemic for four years prior to her intercurrent illness. Another case came to the eye clinic because of a large retinal hemorrhage causing blindness, but had been under treatment for anemia for "years." Five of the cases with a history of anemia of two or more years' duration first noticed symptoms during the postpartum state though there had been no excess bleeding or infection. Many of the cases gave a history of menstrual disorders, often characterized by excessive bleeding for which no local cause could be found. The train of gastric symptoms usually met with where free hydrochloric acid is absent from the stomach secretion, was lacking in many instances. Several cases admitted to flatulence when questioned, but bouts of diarrhea were not encountered.

The patients were not as a rule undernourished, the average weight of 16 patients being 121 pounds. A gain in weight invariably followed successful therapy.

Physical Signs. All patients in the series were women who presented a waxy, bloodless appearance. The sclerotics were pearly white rather than subicteroid in color, and the mucous membranes pallid. In 5 cases the subicteroid appearance of the skin and the well-preserved adipose tissue was such as to suggest pernicious anemia. This appearance is apparently due to the pallor of the skin and the yellow fatty tissue beneath it for none of the cases had any excess of bilirubin in the blood. Examination as a rule revealed no evidence of parenchymatous disease. A systolic heart murmur was present in 9 cases, but without other evidence of cardiac disease. Subacute combined sclerosis of the cord was not demonstrated in any of the cases by the usual methods of examination including pallesthesia and 2 point discrimination tests, though numbness and tingling of the extremities was not an uncommon symptom, occurring in 12 cases.

The spleen was palpable in only 3 cases, reaching just to the costal

margin. In a fourth case it was enlarged to percussion but was not felt. However, in none of these cases was there any increase in the bilirubin content of the plasma or in the urobilinogen in the urine, and this held for the remainder of the series in which no splenomegaly occurred. Glossitis was not observed in any of the cases, though the tongue was frequently described as atrophic at tip and edges. Because of a decided lack of unanimity in opinion concerning atrophy of the tongue in many of the cases the incidence of this sign is problematical. Certainly the glazed tongue of Addison's anemia is seldom seen, though some degree of atrophy is not uncommon.

The Blood. The blood picture in the disease is chiefly remarkable for the marked reduction in the hemoglobin level, without a corresponding fall in the number of erythrocytes. Color indices in the vicinity of 0.5 or 0.6 were commonly observed. One of the most striking facts noted in cases which have been under observation from long periods as from 5 to 7 years was the tendency of the hemoglobin level to remain in the vicinity of 50 per cent, neither improving nor dropping lower unless unfavorably influenced by some complication as pregnancy, menorrhagia, hemorrhoids, etc. This same observation has also been made by Waugh.[10]

The reduction in the erythrocytes was never in proportion to the hemoglobin deficiency. Counts under 3½ millions were seldom encountered, and a majority were in the vicinity of 4 millions (see chart). The platelets were, as a rule, slightly below the normal level but in 2 instances were increased. The leukocytes were nearly always somewhat reduced though normal counts or even slight leukocyte increase was occasionally observed. The differential count of leukocytes showed that the leukopenia was at the expense of the polynuclear cells. In other words there was a relative lymphocytosis. The actual figures may be obtained by referring to the chart.

Evidence of increased hemolysis has not been noted in any of the cases. The bilirubin content of the plasma as determined by van den Bergh tests was always within normal limits. The erythrocytes always averaged slightly below the normal in size, the mean red cell diameter in 19 cases being 7.5 micra as compared with less than 6.5 micra in Dameshek's cases. While scarcely below normal figures for dried cells, this is distinctly less than the average obtained with wet preparations. Variations in size and shape were not remarkable. Stippling and other signs of immaturity as nucleated forms and reticulocytes were not observed.

The cardinal defect in the blood is therefore a deficiency in hemoglobin whether as a result of iron deficiency or failure of utilization has not been determined.

Diagnosis. The diagnosis of idiopathic hypochromemia depends primarily upon the exclusion of possible etiologic factors as chronic

blood loss from peptic ulcer or uterine polypi, tuberculosis, syphilis and other chronic diseases capable of giving rise to a severe secondary anemia. Having ruled out possible causes for anemia, and demonstrated a deficiency or absence of free hydrochloric acid in the gastric contents and the existence of a chlorotic blood picture, the diagnosis of the disease is justified.

At this point there naturally arises a criticism of certain of the cases included in this series as those complicated by colitis, myxedema or chronic cholecystitis. May not the anemia have been a complication of these diseases rather than a primary blood disorder? In the first place achlorhydria is uncommon in these disorders and, second, the time of onset of the anemia was clearly long in advance of the complicating factor. In the case of the patient with chronic cholecystitis the anemia antedated the hepatic symptoms by 4 years. The case with myxedema was allowed to return to a state of hypothyroidism but her hemoglobin showed no tendency to revert to its former low level. The fact is that many women with achlorhydria tend to develop anemia of the hypochromic type. Poor hygienic surroundings, defective diet or such diseases as just discussed act as an additional drain upon the hematopoietic tissues aggravating the state of anemia, or, what is much more likely (and this is borne out by the histories) bring about such a reduction in the hemoglobin level as to seriously incapacitate the patient and drive her to seek treatment. However, the majority of patients develop anemia without any complicating factor and consult the physician because of the symptoms to which it may give rise. In either case the condition is essentially a primary blood dyscrasia.

Differential Diagnosis. *Pernicious Anemia.* Seven of the cases in this series were referred to the clinic as pernicious anemia. The history of paresthesia, the pallor, the achlorhydria and the absence of any cause for the anemia led to the diagnosis of Addisonian anemia in spite of a hypochromic rather than a hyperchromic type of blood picture. The small type of erythrocytes, the absence of bilirubinemia and the complete failure of liver and liver extract were features which separated these cases sharply from the category of pernicious anemia.

Chlorosis. The disease in some respects resembles chlorosis. It is almost always observed in the female sex and the cardinal defect is one of hemoglobin production. On the other hand it affects older women, it runs a very chronic course, and it is unaffected by amounts of iron which rapidly cure chlorosis. Then again hyperchlorhydria is the rule in chlorosis.

Splenic Anemia. In our experience, difficulty has been encountered in ruling out instances of early splenic anemia. One patient, Mrs. W., aged 37 years, with a history of anemia of 3 years' duration, achlorhydria and a nonpalpable spleen failed to improve on treatment. A year later the spleen became palpable and bilirubinemia

and urobilinuria made their appearance. A feature which from the beginning should have raised the question of early splenic anemia was the persistent leukopenia of from 1000 to 3000 leukocytes per c.mm.

Acute Hemolytic Infectious Anemia. Idiopathic hypochromemia may be confused with acute infectious anemia. A series of cases of this disease has recently been reported by Lederer,[15] and 2 cases have come under our observation. The acuteness of the onset, the pyrexia, the bilirubinemia and urobilinuria of acute infectious anemia are the differential points as actual blood pictures may not present marked differences.

Aplastic Anemia. Several of the cases have come to the clinic labeled aplastic anemia. This disease is characterized by a fairly acute and fatal course, normal gastric acidity and usually a hyperchromic type of anemia with thrombopenia and the resulting hemorrhagic phenomena. No great diagnostic difficulties are therefore encountered.

Anemia of Pregnancy. A secondary type of anemia sometimes of a severe degree which is not uncommonly found in pregnancy, may be difficult to distinguish from idiopathic hypochromemia. However, achlorhydria is not a part of the picture and, as Osler[16] has pointed out, anemia of pregnancy disappears rapidly with the termination of the pregnancy or the institution of ordinary iron therapy. These facts were confirmed recently by the studies of Bland, Goldstein and First.[17]

Prognosis. As already mentioned, one of the most striking features of idiopathic hypochromemia is its persistence over long periods without much tendency to improve or become worse and in defiance of ordinary methods of therapy. Pregnancy, infections and debilitating circumstances tend to aggravate the condition, but in our experience have never led to a degree of anemia incompatible with life. The improvement which results from adequate therapy is not maintained unless this treatment is repeated at intervals. This is what is to be expected granted that the underlying defect is a deficiency of hydrochloric acid or is associated with it.

Treatment. The favorable response of 10 cases of idiopathic hypochromemia to fairly large doses of iron and small quantities of a copper salt was reported in the preliminary communication.[1] No hydrochloric acid was given to these cases. Nearly all were ambulatory patients. The treatment was suggested by the experimental observations of Hart, *et al.*,[18] on milk anemia in white rats and later by Whipple's group studying anemia in dogs. The preparation of iron chosen was Blaud's mass. To it was added copper carbonate in the proportion of $\frac{1}{48}$ gr. of the latter to 30 gr. of Blaud's mass. These amounts were incorporated in a soluble capsule together with a small amount of a suitable laxative. The amount prescribed was 1 capsule thrice daily. Larger quantities of the copper salt

were prescribed in 5 cases, in amounts up to 5 gr. daily, but this increase resulted in a mild degree of gastroenteritis characterized by anorexia, abdominal cramps and diarrhea. The reputed toxicity of copper was discussed in the preliminary paper. For control purposes most of the original cases were placed on a preliminary

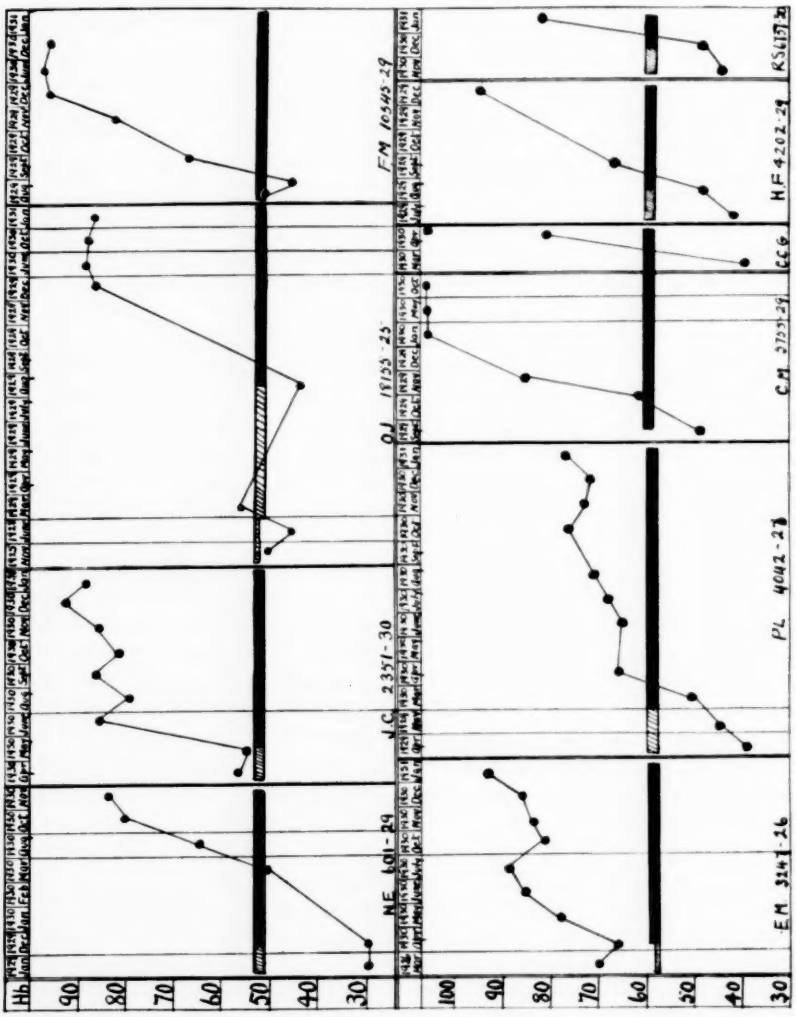


CHART 1.—Effect of treatment on hemoglobin level.

period of treatment by Blaud's mass alone. Sixty grains were given daily. This treatment was persisted in for 4 weeks prior to the iron and copper trial. In 5 cases the control period was much longer than 4 weeks. No hydrochloric acid was given unless the cases proved refractory to the iron and copper mixture. The effect of the iron-copper capsules on the hemoglobin in 19 of the 22 cases

is graphically represented in the charts. Of the 3 cases uncharted, 1 could not be traced, and the other 2 are reported by their family physician to be quite well, though we have not had an opportunity to check their blood. Of the 19 cases recorded in the charts, little need be said. The results are classified as good in 16 cases, fair

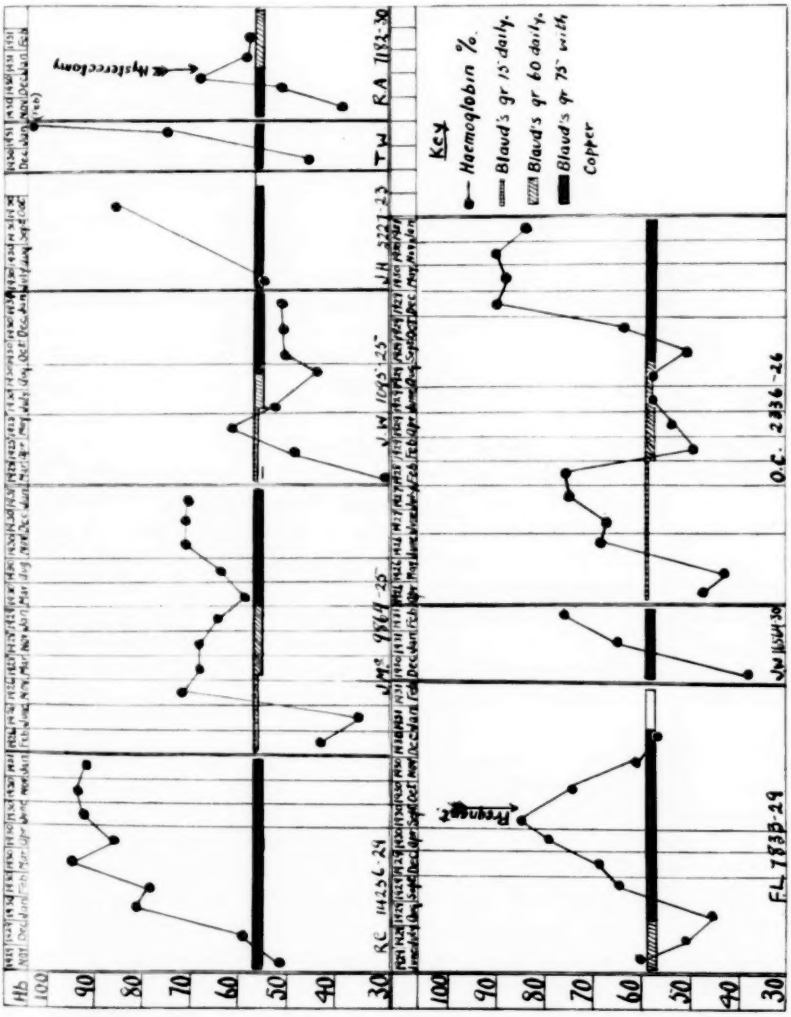


CHART 1.—Effect of treatment on hemoglobin level.

CHART 2.—Effect of treatment on hemoglobin level.

in 1 case and poor in 2 cases. In most instances there was only a slight rise or no improvement in the hemoglobin level on the Blaud's mass while a decided increase in the hemoglobin promptly followed the addition of copper to the mixture. Not the least striking improvement was the patient's color. The appetite returned, and

with it a sense of well-being and a gain in weight. Two cases became pregnant after a sterile period of 5 and 7 years respectively.

The original cases have now been followed for 1½ years since beginning this therapy and all cases showing improvement have maintained this improvement, with the exception of the 2 cases which became pregnant, though there appears to be a tendency for the hemoglobin level to decline unless therapy is repeated at frequent intervals.

There have been 2 failures (J. W. and J. Mc.). These cases have both been anemic for many years—one has been under observation 5 years and the other 7 years. Both have been tried on liver, liver extract, Blaud's mass, the iron and copper mixture, and are now being tried on iron and copper with hydrochloric acid, so far without much success. There has been no complicating factor and a recent complete check-up has not yielded additional information. The superiority of iron and copper therapy over iron alone in the treatment of this disease has been confirmed by Waugh. Giffin and Watkins[20] have failed to obtain results with the independent administration of copper and manganese in such cases. This failure would tend to support the contention that it is the iron which is the necessary hemoglobin building substance, but that it is rendered more available by the action of the combined copper.

The question of the relative efficiency of large doses of Blaud's with and without dilute hydrochloric acid is still being debated. Mettier and Minot believe that iron acts better when given in an acid medium as with dilute hydrochloric acid. Witts, on the other hand, has emphatically stated that the giving of dilute hydrochloric acid with iron in no way enhances its therapeutic value. He has achieved success in treating this idiopathic type of anemia with large doses of iron alone, though improvement began only after the first month of therapy. If this holds true many of our control periods were too short. In 5 cases, however large doses of Blaud's (60 gr.) were given for many months prior to the iron and copper therapy without any improvement in the anemia. Be this as it may, the addition of small amounts of copper would seem to render the iron more readily available as a hemoglobin builder.

In Germany[21] the disease has been treated successfully with ferrum reductum in 1 gm. doses. As Blaud's is only 10 per cent iron this amount of reduced iron corresponds to 154 gr. of Blaud's—a rather heroic dose of iron. Four cases in our series were given capsules containing 1 gm. of reduced iron in order that the results might be compared with the iron-copper therapy. The treatment was stopped when on 2 successive occasions 3 of the 4 patients reported severe abdominal cramps, vomiting and diarrhea, indicating a chemical gastroenteritis. This complication has occurred only once to our knowledge with the capsules of iron and copper, though a mild laxative action has been frequently noted.

No explanation of the mode of action of copper has been offered.

It was originally suggested by Hart, *et al.*, that the copper acted as a catalyst improving the absorption of the iron from the intestinal tract. Whether this is so or whether the copper is absorbed along with the iron and serves in the synthesis of hemoglobin is a problem not likely to be entirely elucidated until more light is brought to bear upon the nature of hemoglobin molecule. Although it is probably true that many cases of idiopathic hypochromemia are benefited by massive doses of iron in the form of Blaud's mass if the treatment is persisted in a sufficient length of time, it would seem that the addition of copper renders the iron more effective, bringing about a more rapid and complete restoration of the blood values.

Summary and Conclusions. Evidence for considering idiopathic hypochromic anemia or hypochromemia as a disease entity is presented and 23 cases of the disease are reported.

The disease is confined to the female and runs a very chronic course with symptoms common to any moderately severe anemia.

The important clinical features are absence or great diminution of free hydrochloric acid in the gastric contents, absence of etiologic factors, a hypochromic blood picture, and a tendency to resist ordinary forms of anemia therapy.

Twenty-one of 23 cases have been treated successfully with a capsule containing Blaud's mass and copper carbonate. Many of these cases had proved refractory to the iron alone before beginning the iron-copper therapy.

NOTE.—The author wishes to acknowledge his indebtedness to Charles E. Frosst & Co. for preparing and donating the capsules, and for other assistance.

NOTE.—Since this paper was submitted for publication, Adamson and Smith have reported identical results from iron-copper therapy in a series of ten cases of this disease. (Can. Med. Assn. J., 1931, **24**, 793.)

BIBLIOGRAPHY.

1. Mills, Edward S.: Canadian Med. Assn. J., 1930, **22**, 175.
2. Watkins, C. H.: J. Am. Med. Assn., 1929, **93**, 1365.
3. Kaznelson, P., Reimann, F., and Weiner, W.: Klin. Wchnschr., 1929, **8**, 1071.
4. Faber, K.: Berl. klin. Wchnschr., 1913, **50**, 598.
5. Weiner, W., and Kaznelson, P.: Folia Hæmatol., 1926, **32**, 233.
6. Spenson, H.: Ugeskrpt. f. Laeger, 1926, **32**, 743.
7. Altschuller, G.: Acta med. scand., 1929, **70**, 119.
8. Lee, R. I., and Minot, G. R.: Nelson's Loose-leaf Medicine, New York, 1928, **4**, 27.
9. Schulten, H.: Münch. med. Wchnschr., 1930, **77**, 385.
10. Waugh, T. R.: Arch. Int. Med., 1931, **47**, 71.
11. Mettier, S. R., and Minot, G. R.: Am. J. Med. Sci., 1931, **181**, 25.
12. Witts, L. J.: Guy's Hosp. Rep., 1930, **80**, 253.
13. Seppänen, A.: Acta med. scand., 1930, Supp. 34, p. 127.
14. Faber, K., and Gram, H. C.: Arch. Int. Med., 1924, **34**, 658.
15. Lederer, M.: Am. J. Med. Sci., 1930, **179**, 228.
16. Osler, W.: British Med. J., January 4, 1919.
17. Bland, P. B., Goldstein, L., and First, A.: Am. J. Med. Sci., 1930, **179**, 48.
18. Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A.: J. Biol. Chem., 1928, **77**, 797.
19. Elden, C. A., Sperry, W. M., Rabscheit-Robbins, F. S., and Whipple, G. H.: J. Biol. Chem., 1928, **79**, 577.
20. Giffin, H. Z., and Watkins, C. H.: J. Am. Med. Assn., 1930, **95**, 587.
21. Barkan, G.: Klin. Wchnschr., 1923, **2**, 1748.

REVIEWS.

HYPERTENSION AND NEPHRITIS. By ARTHUR M. FISHBERG, M.D., Associate Physician to Beth Israel Hospital; Adjunct Physician to Mount Sinai Hospital, New York City. Pp. 619; 38 illustrations, 1 colored plate. Philadelphia: Lea & Febiger, 1931. Price, $6.50.

THIS book is primarily a statement for the practitioner of our present knowledge concerning hypertension and the various forms of nephritis. The earlier chapters take up the pathologic physiology of renal function; the tests of renal function; albuminuria and urinary casts; edema, uremia; arterial hypertension; hypertensive encephalopathy and hypertensive retinopathies. Then the various types of kidney disease are considered, the classification used being practically that of Volhard and Fahr. The presentation is thorough and complete, with numerous references to original sources and careful statement of controversial points. In addition to a thorough knowledge of his subject, the author brings to his task sound judgment and an ability for clear and forceful expression. Ample testimony of this is the fact that the first edition was exhausted within a year of its publication. The new edition has been thoroughly revised and includes much new material that accounts for an increase of 53 pages. The book is one that is highly to be recommended both to internists and to general practitioners.

R. K.

ACCIDENTAL INJURIES. By HENRY H. KESSLER, A.B., M.D., F.A.C.S., F.A.P.H.A., Medical Director, New Jersey Rehabilitation Clinic. Pp. 718; 157 illustrations. Philadelphia, Lea & Febiger, 1931. Price, $10.00.

THE rapid development of industrial surgery and the medical aspects of public liability have formed a new field in medical literature. In the last few years this field has been filled rapidly by the publication of books which set forth the experiences of those who deal with large numbers of accidental injuries. They represent the most authoritative analysis of the subject by which the practitioner, industrial surgeon or the compensation board may base the prognosis and treatment. Kessler, due to his wide experience in this

type of work is particularly fitted to write a valuable book on this subject. After reviewing the history and the medicolegal aspects of compensation insurance, he takes up individually injuries to various parts of the body. He discusses the relation of injury to disease, the probably period of disability resulting from the individual injuries and the method of evaluating the disability produced. An excellent discussion is given of traumatic neurosis and of methods for detection of malingering.

An extensive section is given on occupational disease, in which are set forth the laws in the various states on the subject. Lead, benzol, mercury, arsenic, radium and other forms of poisoning are discussed as well as other occupational diseases, such as anthrax, silicosis, etc.

The last chapter on rehabilitation of the physically handicapped certainly deserves commendation.

The book is well illustrated and at the end of each chapter are given extensive references on the subject which has been discussed. Court cases are often cited briefly to illustrate specific points.

Dr. Kessler's style is analytical and statistical, and the opinions which he expresses therefore bear the weight of authority. The work should find a large field among those who are in the practice of traumatic and industrial medicine and surgery. L. F.

DISCOVERING OURSELVES. By EDWARD A. STRECKER, A.M., M.D., and KENNETH E. APPEL, PH.D., M.D. Pp. 306; 28 illustrations. New York: The Macmillan Company, 1931. Price, $3.00.

INTROVERTS and extroverts, the subconscious, transference, rationalization, inferiority and many other complexes (by the way, why cannot we hear more of superiority complexes?) are today such frequently used terms on the street and stage that one may feel sure that the public is on its way to becoming "mental-hygienically conscious," to continue the cacophonic jargon. Nevertheless the superficiality of such knowledge is in danger of making it the proverbial dangerous thing. "Know thyself" may well be considered the essence of wisdom, yet the "Teach thyself," that is hoped for in reading such a book in a complex field like this should certainly be supplemented by personal contact with expert instructors if the patient is to receive maximum benefit. With this qualification, simple yet sound and thoughtful books such as Riggs' "Intellectual Living," Osler's "A Way of Life," James' "The Will to Believe," and the present one written by authorities on their subject, are all the more needed to help in the preservation or restoration of normal mental mechanics. E. K.

THE HISTORY OF PÆDIATRICS. By GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LOND.), Professor of Diseases of Children, King's College, London. Pp. 526; 12 illustrations. New York: Oxford University Press, 1931. Price, $8.00.

MANY, even of middle age, who learned of Still's Disease in their student days, may be surprised that its first describer is still with us as Professor of Diseases of Children at King's College, London, and active. The present work in fact had to be created in "rapt hours snatched from the heavy demands of busy practice, a *πάρεργον* indeed."

Beginning with Hippocrates, the author pleasantly portrays the progress of the study of diseases of children through the ensuing 2300 years from a combined chronologic and biographic point of view. Like the history of general medicine, it portrays the activities of the classical period, the stagnation of the Dark Ages, the revival of the Renaissance, and the chief milestones of progress from then to the end of the eighteenth century. One cannot but regret that the author did not chose to pursue his topic into the important contributions of the nineteenth century. A companion to, rather than a rival of, Ruhräh's "Pediatrics of the Past," Still's History finds room for over 50 names not included in the Anthology, while of those included by Ruhräh, only Areteus, Wurtz and Plater are omitted from Still's Table of Contents. A list is given of 213 Inaugural dissertations scattered over three centuries; but how easy would it be to double such a list: from the Elzevir press alone one could cull many a "De rachitide," "De Cholera Morbus," "De Tussa Convulsiva," "De Hydrocephalo," etc., most of which would show more mimicry than merit. In spite of a slight tendency toward biographic lexicography the book affords many a pleasant hour's reading and we are glad that the author "was too much in love with my subject to jilt it" when he came in contact with previous explorations in the same field. E. K.

ZEHN JAHRE FORSCHUNG AUF DEM PHYSIKALISCH-MEDIZINISCHEN GRENZGEBIET. By O.S. PROF. DR. FRIEDRICH DESSAUER, Direktor des Institutes. Pp. 403; 190 illustrations. Leipzig: Georg Thieme, 1931. Price, M. 36.

THIS work is a report of the results obtained in an institute designed for the study of the application of physics to medicine. Interest in the book is therefore narrowed to two groups, physicists, interested in apparatus and methods, and clinicians interested in certain special problems.

Of greatest interest to general medicine is the subject to which

most attention is paid in the volume—the study of the effect of air carrying a positive or negative electric charge. The problem of producing and controlling exact conditions for the experiment is discussed at length with descriptions of apparatus and methods. Increased blood pressure is lowered by inhalations of negatively ionized air; the best results in cases of climatic and essential hypertension. Positive charged air acted unfavorably and increased the blood pressure. Subacute and chronic "rheumatic" complaints reacted with increased pain and at times, objectively, with joint swelling; in a certain number of cases it is believed that a favorable therapeutic result was attained.

Most interesting is a suggestion of Dessauer, that an unknown agent in the air is perhaps the active factor, the ionization acting as an activator.

The remainder of the book is devoted to diverse problems of which the most important is a basic discussion of the biologic action of radiant energy. J. S.

THE PHYSICIAN OF THE DANCE OF DEATH. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. Pp. 142; 92 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $7.50.

FEW of the thousands of tourists who annually cross the Mühlenbrücke at Luzerne can have failed to have been interested in the quaint triangular representations of Meglinger's Totentanz and few cultured people have not at least some appreciation of Holbein's "Imagines Mortis." Never, however, has the underlying idea and its various manifestations been more accurately and entertainingly told than in the present book, reprinted from articles in the *Annals of Medical History*. The Danse Macabre, or Totentanz, has held the imagination of Europeans for over 500 years, from the earliest known example of 1424 in the Cimetière des Innocents in Paris to the numerous recrudescences brought out by the World War. Taking form at a time when plague and pestilence and a very vivid hell were everpresent horrors, it has been variously explained as the popular expression of the early Christian *memento mori*, the superstition of the midnight dance of the churchyard dead, or, as the author prefers, the neurotic response of an emotionally unstable age by taking actual pleasure in its very fear of death. The later introduced element of satire on social equality and even political and religious satires also played their parts in the sixteenth century. The author's emphasis on the physician of the series reveals not only the physician's changing costumes over 500 years but also something of his social standing and of lay concepts of the status and progress of

medicine during a long period. With the changed modern philosophy toward death, such as the author's view of its being a normal termination of an involution period—"the Totentanz mythus awaits a new birth." E. K.

THE DIAGNOSIS AND TREATMENT OF BRAIN TUMORS. By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis. Pp. 396; 224 illustrations, 10 in colors. St. Louis: C. V. Mosby Company, 1931. Price, $10.00.

SACHS has written a very useful book on the diagnosis of brain tumors. There has not been such a work available to medical students and those not familiar with the field. This work attempts to supply the need.

The work is logically carried out. There is an elementary chapter on the anatomy of the nervous system, giving the essential details necessary for diagnostic purposes. There is a good chapter on methods of examining the nervous system, and a useful chapter on the surgical pathology of brain tumors. Following these elementary chapters there follows a discussion of the signs and symptoms of tumors in the various regions of the brain. The chapter on the differential diagnosis of brain tumors and conditions which may simulate them is interesting, and the final chapter on operative technique will prove useful in giving an understanding of neurosurgical methods to those who are unfamiliar with them.

The book suffers from being too elementary. For this reason it will prove much more useful to medical students than to specialists in the field of neurology or neurologic surgery. B. A.

PRIMARY SYPHILIS IN THE FEMALE. By THOMAS ANWYL DAVIES, M.D. (LOND.), Director of the Whitechapel (L. C. C.) Clinic. Pp. 120; 25 illustrations, 17 in colors. New York: Oxford University Press, 1931. Price, $4.00.

THIS monograph is a work of distinction in its field, both in matter and format. The author draws on probably the largest and most thoroughly studied material of its kind in existence, to correct many misimpressions in regard to the onset of syphilis in the woman, a problem full of significance for both individual and public health. From a massive series of 584 personally examined cases in the key clinic of the British venereal disease service, St. Thomas' Hospital, the author shows that the chancre in the woman is internal in 45 per cent of cases, and usually on the cervix, a point raising most important questions as to the mechanism of infections and the nature of the infecting agent in the male. The symptoms

of primary syphilis in the woman, the types of lesions, the differential considerations, the confusion with carcinoma and gumma, non-venereal vaginal conditions, such as trichomonas infections, are all dealt with in systematic and terse fashion, and with gratifying completeness. The photography especially, to one who knows the regional difficulties, is remarkable, and, while the Reviewer holds in general no brief for colored plates, these are very much above the average and really instructive. The review of the literature carried through the text discussion is clear, discriminating and extensive. It is interesting to see how large an error based on impression of an occasional case may loom. The book can be commended to practitioners and, of course, most emphatically to gynecologists, venereologists and officers of public health clinics who need it as a desk reference. J. S.

BOOKS RECEIVED.

NEW BOOKS.

Cosmic Consciousness. By Richard Maurice Bucke, M.D., Formerly Medical Superintendent of the Asylum for the Insane, London, Canada. Pp. 384; 1 illustration. New York: E. P. Dutton & Co., Inc., 1931. Price, $5.00.

Bedside Interpretation of Laboratory Findings. By Michael G. Wohl, M.D., Associate Professor of Experimental Medicine, Temple University Medical School, Philadelphia. With an Introduction by Joseph McFarland, M.D., Sc.D., Professor of Pathology, University of Pennsylvania. Pp. 321; 133 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $6.00.

Encephalitis Lethargica, Its Sequelæ and Treatment. By Constantin von Economo, Professor of Psychiatry and Neurology in the University of Vienna. Translated and adapted by K. O. Newman, M.D., Pathologist to the Oxford County and City Mental Hospital, Oxford. Pp. 200; 21 illustrations. New York: Oxford University Press, 1931. Price, $6.00.

Cutaneous X-ray and Radium Therapy. By Henry H. Hazen, A.M., M.D., Professor of Dermatology, Medical Department of Georgetown University. Pp. 166; 28 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $3.00.

The Causation of Chronic Gastro-duodenal Ulcers. A New Theory. By J.-Jacques Spira, M.R.C.S. (Eng.), L.R.C.P. (Lond.), with an Introduction by Sir Humphrey Rolleston, Bart., G.C.V.O., K.C.B., Physician in Ordinary to H. M. the King. Pp. 78. New York: Oxford University Press, 1931. Price, $2.50.

Asthma and Hay Fever in Theory and Practice. In three parts. *Part I. Hypersensitiveness, Anaphylaxis, Allergy.* By Arthur F. Coca, M.D., Professor of Immunology, Cornell University Medical College. *Part II. Asthma.* By Matthew Walzer, M.D., Instructor in Applied Immunology, Cornell University Medical College. *Part III. Hay Fever.* By August A. Thommen, M.D., Lecturer in Medicine, University and Bellevue Hospital Medical College. Pp. 851; 95 illustrations and 7 charts. Springfield, Ill.: Charles C Thomas, 1931. Price, $8.50.

Modern Proctology. By MARION C. PUTTT, M.D., L.R.C.P., S. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., Associate in Surgery, Emory University School of Medicine, Atlanta. Pp. 404; 233 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $8.00.

Fractures of the Jaws. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-facial Surgery, Graduate School of Medicine, and of Clinical Maxillo-facial Surgery, School of Dentistry, University of Pennsylvania, and LAWRENCE CURTIS, A.B., M.D., D.D.S., Assistant Professor of Maxillo-facial Surgery, Graduate School of Medicine and School of Dentistry, University of Pennsylvania. Pp. 180; 177 illustrations. Philadelphia: Lea & Febiger, 1931. Price, $4.50.

United Fruit Company Medical Department 19th Annual Report, 1930. Pp. 276; 31 illustrations.

The Great Physician. A Life of Sir William Osler. By EDITH GITTINGS REID. Pp. 299; 10 illustrations. New York: Oxford University Press, 1931. Price, $3.50.

Medicine, Science and Art. By ALFRED E. COHN. Pp. 212. Chicago: The University of Chicago Press, 1931. Price, $4.00.

Injuries and Sport. By C. B. HEALD, C.B.E., M.A., M.D. (CANTAB.), M.R.C.P. (LOND.), Physician, with Charge of Electro-therapeutic Department, Royal Free Hospital. Pp. 543; 380 illustrations. New York: Oxford University Press, 1931. Price, $8.00.

The Medical Clinics of North America, Vol. 15, No. 1 (Mayo Clinic Number—July, 1931). Pp. 263; 56 illustrations. Philadelphia: W. B. Saunders Company, 1931.

Diagnosis in Joint Disease. By NATHANIEL ALLISON, M.D., F.A.C.S., Professor of Surgery, in charge of Division of Orthopedic Surgery, University of Chicago, and RALPH K. GHORMLEY, M.D., Associate in Orthopedic Surgery, The Mayo Clinic. Pp. 196; 215 illustrations—11 in color. New York: William Wood & Co., 1931. Price, $9.00.

Medical Jurisprudence. By CARL SCHEFFEL, PH.B., M.D., LL.B. Pp. 313. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $2.50.

Breast-Feeding. By MARGARET EMSLIE, M.D., CH.B., Late Senior Assistant Medical Officer for Maternity and Child Welfare, County Borough of Croydon. Pp. 142; 6 illustrations. New York: Oxford University Press, 1931. Price, $2.00.

NEW EDITIONS.

Manual of Surgery, Vol. 1. General Surgery. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 574; 176 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, $3.80.

Diseases of the Gums and Oral Mucous Membrane. By SIR KENNETH GOADBY, K.B.E., M.R.C.S., L.R.C.P., D.P.H. (CANTAB), Lecturer on Bacteriology of the Mouth, Dental Department, University College Hospital. Pp. 496; 146 illustrations. Fourth edition. New York: Oxford University Press, 1931. Price, $13.00.

Practical Zoölogy. Revised Edition. By ROBERT W. HEGNER, PH.D., Professor of Protozoölogy, Johns Hopkins School of Hygiene and Public Health. Pp. 561; 332 illustrations. New York: The Macmillan Company, 1931. Price, $1.80.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
W. S. THAYER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Coronary Artery in Health and Disease.—HERRICK (*Am. Heart J.*, 1931, **6**, 589), in the latter part of his Harvey Lecture, discusses the theories that have been advanced to explain the mechanism of production of heart pain. He writes that there are two prevalent theories to explain the causation of this pain: The one, the aortic theory, holds that pain is due to stretching of the diseased wall of the great vessel. Allbutt was the first serious protagonist of this idea, and after him Wenckebach, Schmidt and Vaquez. The older theory, the one that has been prevalent since the time of Parry and Jenner, maintains that the explanation of the symptom complex lies in perversion of the function of the coronary artery or the muscle supplied by that artery, or by both. In substantiation of this thesis, the author advances arguments which have been proposed in the past, and in addition he suggests that a few of the more recent and more exact physiologic and chemical studies may add additional corroboration to the coronary theory. The arguments that appeal to him especially, and they are more or less old arguments, are, that the negative finding of coronary disease in a certain number of cases may be explained on the basis of incomplete examination of these vessels or, if this is not the explanation, that the disease itself is due to a disturbance of function and the anatomic lesion is not the disease; that angina is very infrequently found with auricular fibrillation, it is rare with "chronic myocarditis" and it is extremely unusual to have anginal attacks when the patient is suffering from far-advanced syphilitic aortitis unless the coronary mouths are involved by this process; that the nitrites and theobromin compounds are dilators of coronary vessels and relieve pain; that epinephrin occasionally provokes anginal attacks in patients given this drug if they are subject to such attacks,

whereas in the young individual with coronary arteries which presumably are not abnormal these injections do not produce pain. A somewhat more modern concept and argument in favor of coronary disturbance is that hypoglycemia, produced by insulin, occasionally produces anginal distress in those subject to angina, as a result of the still further reduction of nutrition to the heart muscles as a result of arterial narrowing; in severe anemia a diminished amount of oxygen to the heart muscle under stress may produce pain; in hyperthyroidism anginal pain may occur in those with damaged coronary arteries because the heart muscle cannot receive a sufficient quantity of blood to meet the requirements of increased metabolism. The electrocardiographic evidence obtained during periods of attacks exhibits variations in ventricular complexes which disappear following the attack and would seem to indicate transitory changes in the heart muscle. In a certain number of instances of Raynaud's disease the vasomotor phenomena have been correlated with angina, and, lastly, of the arguments to substantiate his ideas, the author is rather inclined to the opinion that animal experimentation would indicate that temporary occlusion of the coronary brings on pain. The author is not dogmatic nor is he assertory. He gives the impression that it is largely a matter of opinion as to which view is accepted concerning the cause of anginal pain, but he states definitely that it is only through coöperation of the internist and pathologist, the experimental physiologist and the electrocardiographer that it would be possible to pile up evidence which would show conclusively just how anginal pain is produced.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Gastric Syphilis.—O'Leary (*Am. J. Surg.*, 1931, **11**, 286) report that 89 of a group of 151 patients with gastric lesions and syphilis were found to have gastric syphilis. These were selected from among approximately 25,000 patients with syphilis. The diagnosis was based on the combined results of prolonged therapeutic tests, histopathologic studies, morphologic changes in the roentgenologic characteristics and restoration of gastric function. The demonstration of the existence of other evidence of clinical syphilis is not pertinent to the diagnosis of gastric syphilis. Of the 89 patients with gastric syphilis 73 per cent had positive Wassermann reaction of the blood as the only other evidence of syphilis and 6 per cent had negative serologic reactions. The incidence of clinical signs of syphilis was almost as high in these cases with gastric carcinoma (16 per cent) as it was in those with syphilis of the stomach (27 per cent). Recognition of the Spirochæta pallida in excised gastric tissue as the conclusive means of diagnosis is a diagnostic requirement demanded by the scientific purist. The author would prefer to see among the diagnostic criteria for gastric syphilis one demanding a histopathologic study to eliminate carcinoma. Although

the Spirochæta pallida may be demonstrated in the gummatous type of gastric ulcer, in cases of diffuse syphilitic fibrosis the organism has not as yet been recognized. Numerous instances of the bizarre character of both the clinical and microscopic features of gastric syphilis merely confirm the knowledge that syphilis is a protean disease. The result of treatment in the fibrosed syphilitic stomach is unsatisfactory and plastic gastric operation offers slight help. As in all forms of syphilis, early diagnosis and early institution of treatment are rewarded by a higher incidence of cure than is obtained otherwise, a fact forcibly emphasized by this study.

Spondylitis Deformans.—Kleinberg (*Arch. Surg.*, 1931, **22,** 485) writes that spondylitis deformans is a chronic disease of the back, characterized by increasing stiffness and deformity of the spine, backaches, pains in the head, chest or extremities and impairment of health. Although there are numerous causes of this disease, the final pathologic change is the same in all varieties. The most disabling feature of this disease is the flexion deformity of the spine. Treatment, to be effective, must be instituted before there is complete bony ankylosis of the spine. The deformity can be corrected, or at least reduced by continuous treatment on a convex frame, supplemented by physiotherapy, stretching of the back and voluntary corrective exercises. Following the correction of the deformity a favorable result can be assured only by a long period of support of the back in a spinal brace.

Attitudes Associated With Lesions About the Hip Joint.—Hart (*Arch. Surg.*, 1931, **22,** 463) states that the attitudes of the following lesions about the hip are discussed, namely, infantile scurvy, rickets and syphilitic epiphysitis associated with pseudoparalyses; tuberculosis of the hip, spontaneous or pathologic dislocation of the hip; septic arthritis of the hip; chronic deforming arthritides, epiphyseal coxa vara or separation of the upper femoral epiphysis; traumatic dislocations of the hip; malum coxæ senilis or hypertrophic arthritis of the hip and fracture of the neck of the femur. Certain lesions about the hip joint present fairly constant attitudes of the lower extremities and have definite relations to age periods. There are a number of factors that determine the attitude of the lower extremities; the factors that determine the malposition in an individual case cannot always be satisfactorily explained. A correct interpretation of the attitude of the lower extremities cannot be made unless the pelvis is placed in the normal anatomic position with reference to the transverse and horizontal plane and the lumbar spine is flat. The frog attitude in a child should lead the physician to suspect one of the pseudoparalyses associated with rickets, scurvy or syphilitic epiphysitis. The position of instability of the hip joint, flexion, adduction, internal rotation, is productive of spontaneous dislocation and should be considered a dangerous attitude. Epiphyseal coxa vara is a hazard of adolescent life and fracture of the neck of the femur is a hazard of old age. The attitude of the involved extremity in each condition is similar, *i. e.*, abduction and external rotation. Infection of the hip joint presents a constant malposition of flexion combined with either abduction and external rotation or adduction and internal rotation.

Prostatic Abscess.—Sargent and Irwin (*Am. J. Surg.*, 1931, **11**, 334) say that in any acute prostatic inflammation there is complete safety in waiting until careful observation has permitted a definite diagnosis of frank abscess formation. Both prostatic lobes should be opened whether or not the signs indicate bilateral abscess formation. Any method involving opening of the abscess into the posterior urethra entails unnecessary risk of persisting urethritis from false cavity formation. Drainage through external urethrotomy unduly lengthens morbidity, favors the development of complicating epidymitis and entails the unnecessary risk of a more or less persistent urinary fistula. No method offers greater freedom from complications and sequelæ or more certain cure of the disease than that of radial perineal dissection with posterior prostatotomy.

Periosteum.—Leadbetter (*Arch. Surg.*, 1931, **22**, 754) declares that autogenous periosteum has a definite tensile strength which does not vary when it is brought into contact with free body fluids. It is easily obtained from the broad anterior surface of the tibia. If care is taken in the removal of the periosteum to elevate the small particles of the outer layer of the cortex, it is definitely osteogenic when placed in contact with cortical bone. Periosteum proliferates best when the grafted bone is thoroughly immobilized. Its proliferation in immobilized bone is rapid and early. It does not interfere with the circulation in the fragmented ends, but rather increases the circulation of this region, thereby offering an aid to the formation of late callus. The use of the periosteal suture allows mobilization of the fractured extremity at an early date.

Mixed Tumors of the Parotid Gland.—Merritt (*Am. J. Surg.*, 1931, **25**, 507) claims that the treatment of mixed tumors of the parotid gland is largely in the hands of the radiologist, high voltage roentgen therapy being a useful adjunct to radium in these cases and is generally indicated. While a small encapsulated tumor may be successfully excised, it appears from the accumulated evidence that implanted radium will accomplish equally as good results. A combination of surgical removal and irradiation by either radium or Roentgen ray is illogical. If the former is adequate, the latter is superfluous. A failure to destroy the tumor by implanted radium or radon at the initial attempt, does not induce the serious complication of increased malignancy which frequently follows in adequate surgical removal. Additional radium treatments may be given until maximum result is obtained.

Perinephritic Abscess.—Birdsall (*J. Urol.*, 1931, **25**, 405) says that 11 cases of perinephritic abscess in this series followed infection, extrarenal in origin. In 4 cases where the abscess was renal in origin, 2 were secondary to renal tuberculosis, 1 to renal lithiasis and 1 to tumors of the kidney. In 1 case there was no etiology ascertainable. Perinephritic abscess of extrarenal origin, in most cases, is the result of hematogenous metastasis of the infecting organisms to the renal cortex followed by cortical abscess with direct extension to the perirenal tissue. Perinephritic abscess may also result from lymphatic metastasis of the infection. The most common organism found is the Staphylococcus aureus. There were no hospital deaths.

THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.,
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,
AND
SOMA WEISS, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Treatment of Obesity With Thyroxin.—Because of the widely varying amounts of thyroid preparation advocated for the treatment of obesity, HELLFORS (*München. Med. Wchnschr.*, 1931, No. 20, 826) undertook a reinvestigation of the problem. The cases studied exhibited pronounced obesity. Constant weight on a standard diet was maintained during a control period after which initial doses of 0.5 mg. of thyroxin were administered three or four times daily by mouth. The frequency of administration was raised to five or six times daily depending on the clinical effect of the drug. Without exception, the subjects began to lose weight slowly within 2 or 3 days after the initial administration. With a daily dose of 2 mg. of thyroxin there was an average loss of 0.2 to 0.3 kg. daily. No diuresis was noted. The general condition of the patients remained good although the basal metabolism usually rose 30 to 40 per cent. The total amount of thyroxin used for the individual patient varied from 18 to 60 mg. The total loss of weight varied from 3 to 7 kg. within 17 days. Temporary manifestations of hyperthyroidism were observed only in cases where the dosage was high. A comparison of various preparations of thyroxin from different pharmaceutical houses showed considerable divergence. Thus 0.5 mg. daily of thyroxin "Henning" produced an average rise of 2 per cent in the basal metabolism; 2 mg. daily of thyroxin "Schering," on the other hand, raised the metabolism only 1 per cent; while 1 mg. daily of thyroxin "Hoffmann-LaRoche" caused a rise of 1 per cent. The carbohydrate metabolism, as judged by sugar-tolerance curves, remained uninfluenced by thyroxin. There was a rise of as much as 30 per cent in the lymphocyte counts at the height of the treatment. No changes were apparent in the circulatory system. The earliest manifestation of overdosage was mental irritability. Perspiration, tremor and changes in menstruation appeared later.

Muscle Extract in the Treatment of Angina and Intermittent Claudication.—KORACH (*München. med. Wchnschr.*, 1931, No. 12, 473) reports on the therapeutic effect of a muscle extract called "Myol" in 70 cases of angina pectoris. Sixty cases of this group suffered from true angina and 10 from pseudoangina. They had received no other treatment. Because the beneficial effect of oral administration is slow and gradual, this channel of administration was not used. Fifteen or 20 minutes after subcutaneous and even more promptly after intramuscular and intravenous administration of the extract, there was a

distinct improvement in the patient's condition. The pain became less intense and the patients were able to move about comfortably. The objective changes were a decrease in the degree of tachycardia and a lowering in the blood pressure of from 10 to 30 mm. of mercury. The capacity to walk increased in cases suffering from anginal pain on moderate exertion. The duration of the effect of a single injection was 24 hours. Following this period the complaints returned but with less intensity. In addition, the muscle extract was also found beneficial in cases with intermittent claudication. In a number of instances the daily administration of the extract was changed after 3 weeks to injections every alternate day. Later the clinical improvement was sufficiently great to make oral administration satisfactory. The author claims that the beneficial effect of the extract is not due to a nonspecific protein reaction, since the cases that responded beneficially to the extract did not respond to protein therapy.

Digitalis Dosage.—WEESE (*Deutsch. Med. Wchnschr.*, 1931, **57**, 625) presents the results of a series of studies employing a standardized form of Starling's heart-lung preparation into which various surviving organs may be introduced at will for perfusion. He was able to establish the fact that the perfused heart of the cat removed quantitatively from the perfusion fluid a fixed amount either of digitoxin or strophanthin in relation to its own weight. This amount was constant for different hearts and was the minimal lethal dose. The amount removed was characteristic for each glucoside and bore a fixed relation to the minimal fatal dose for the cat when administered intravenously. For digitoxin the heart removed by $\frac{1}{16}$ of the minimal lethal intravenous dose as its own minimal lethal dose by perfusion; for strophanthin the ratio was $\frac{1}{11}$. The author confirms the well known fact that the digitalis glucosides disappear almost immediately from the blood stream and he concludes that the remaining $\frac{15}{16}$ of the fatal dose of digitoxin or $\frac{10}{11}$ that of strophanthin are removed by immediate fixation in other organs of the body following intravenous injection. By the perfusion of various organs including voluntary muscle and the injection of doses of the glucosides into the circulation leading to these organs so that they must first pass through the perfused organ before reaching the heart, he establishes the fact that all tissues of the body except the lungs participate in this immediate adsorption of the glucosides, the most important being voluntary muscle and the liver. He also shows that the rate of absorption by the heart is influenced by the concentration of the glucosides, although this does not alter the total amount absorbed. Furthermore, the proportional utilization of the glucosides by the heart as compared to the remaining tissues of the body increases as the concentration of the drug in the blood stream diminishes. Thus the maximal effect upon the heart is best secured by slow intravenous injection. Dilatation and hypertrophy of the heart increase its capacity to absorb the glucosides, probably by increasing its surface area and that of its vascular system. Contrary to this, exhaustion of the heart, especially by reducing the soluble phosphatids and calcium salts, diminishes its capacity to bind the glucosides. Inasmuch as these latter conditions are believed to prevail in the presence of cardiac disease, it is suggested that they tend to offset the great susceptibility of the heart which results from its dilatation and hypertrophy.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Evaluation of the Results of Tonsillectomy and Adenoidotomy.—SELKIRK and MITCHELL (*Am. J. Dis. Child.*, 1931, **42**, 9) point out that there are 11 methods of approach to a study of the effects of tonsillectomy and adenoidotomy. Their study was an attempt to use the method commonly employed by other investigators, but with a smaller group of children, so that more intensive study of them could be made than is possible in dealing with a larger group. At first they planned to compare the changes in their group of 130 tonsillectomized children with those of a similar group of controls, but this plan was abandoned because the group was rather small, but still more because it was deemed faulty for other reasons. Nevertheless, because of the thoroughness of the investigation it was decided to present the report. They found that 3 years after tonsillectomy there was a lessened incidence of colds, nasal obstruction and sore throat, while sinus infection, headache and growing pains were increased in frequency. As a criticism of their own study and that of many others, they note certain modifying factors to which no attention or too little attention is paid. These are age, sex, race, heredity, financial class, season, the effect of adenoidotomy alone, length of observation after operation, source from which the history was obtained, incidence of tonsillectomy in the community at large, and the suitability of the control group. The neglect of these factors often invalidates the conclusions. There are several methods of approach in evaluating the results. The method of choice varies with the symptoms studied. The method of studying a large number of symptoms and pathologic conditions simultaneously usually results in superficiality. Separate and intensive studies of a single symptom in relation to tonsillectomy have been made mainly on the rheumatic syndrome and probably offer the best means of approach of studying the other symptoms. Many of the symptoms and conditions popularly supposed to be associated etiologically with diseased tonsils are those in which the natural course and incidence, regardless of the effect of tonsillectomy, are not known. Many of them, also, are affected by other factors than tonsillectomy in an as yet unknown manner. It would seem that the conclusions drawn from some of the studies which are widely quoted as showing the effects of tonsillectomy are decidedly open to question because of the failure to consider other factors in evaluating the results.

Mineral Metabolism in Late Rickets.—STEARNS, OELKE and BOYD (*Am. J. Dis. Chil.*, 1931, **42**, 88) followed the progress of two girls by means of roentgenograms and chemical studies over a period of several months. They noted definite roentgenologic evidence of calcification

of bone. Both children during the period of healing rickets, retained ample quantities of calcium and phosphorus. The manner of excretion of these elements was similar in both children to that observed in infantile rickets with the exception that the urinary excretion of calcium remained low during the period of healing, instead of increasing, as has been noted usually in healing of infantile rickets. The acid-base relationships of the urine and the retention of total fixed base of these children were not conspicuously different from those of a child of the same age, who had no abnormalities of the bone. The serum calcium in each child was at all times within normal bounds. The serum inorganic phosphorus of each child remained consistently low, between 2 and 3 mg. per hundred cc., during the entire period of study, although the rachitic condition was markedly improved in both children.

The Treatment of Chorea by Induction of Fever.—Sutton (*J. Am. Med. Assn.*, 1931, **97**, 299) says that the evaluation of any method of treating a disease like chorea, which has several grades of severity, and which, when untreated, has such a variable duration, is very difficult. Many patients apply at a hospital after weeks or months of illness. Others come within a week or two of the onset, and occasionally a case develops in the ward. It is well known that the average attack improves with rest and quiet and is over in from 6 to 10 weeks, even without any other treatment. It is equally well known that the slightest twitchings of a mild attack may persist for months. Sometimes an attack will continue in all of its severity for a long period. Formerly the author was accustomed to isolate the patients as well as possible. They were kept quiet in bed until all choreiform movements were gone. Various drugs and other methods of treatment, such as arsenic, calcium bromide, salicylates, thyroxin and cold packs were tried at different times without noticeable effect on the course of the disease. The present method of treatment has changed the outcome so that it is possible to expect the average patient to be ready for discharge in about 3 weeks after admission, unless the discharge is delayed by some other illness, by operation such as tonsillectomy, or by waiting for a vacancy in a convalescent home. This new method has been used for too short a time to warrant any comment on the possible effect on recurrences or the development of heart disease. The author treated 24 cases of chorea with intravenous injections of typhoid-paratyphoid vaccine as a means of producing fever. The results thus far were good. There was prompt cessation of the symptoms, and the course of the disease seemed to be greatly shortened. In the cases reported the average duration of treatment was from 8 to 9 days. A drug that has been used in the treatment of chorea is phenyl-ethyl-hydantoin. Its benefit is also derived from the production of a febrile phase. The advantages of the typhoid-paratyphoid vaccine over this drug are that the febrile reaction can be produced immediately without the necessity of waiting for a period up to 2 weeks for intoxication to develop. All cases respond to the typhoid-paratyphoid reaction while not all cases develop the intoxication and fever with the phenyl-ethyl-hydantoin, even when given over long periods. The typhoid-paratyphoid vaccine has not caused any complications such as severe skin eruptions, agranulocytosis, bronchopneumonia and nephritis, which have been described

with phenyl-ethyl-hydantoin. By increasing the dose of the vaccine, or when giving it again several weeks after a course of injections, fever can always be produced.

The Antirachitic Potency of the Milk of Cows Fed Irradiated Yeast or Ergosterol.—Hess, Lewis, McLeod and Thomas (*J. Am. Med. Assn.*, 1931, **97**, 370) found that cow's milk was made highly antirachitic by means of supplementing the fodder with irradiated ergosterol or with irradiated yeast. These milks of various potencies were given to a large series of infants during the winter. By this means rickets was prevented except in its minor manifestations, and roentgenologic rickets did not develop. In cases in which rickets was already present, the milk brought about calcification within a month. From the point of view of the number of antirachitic rat units fed to the cow, the irradiated yeast induced a more potent milk than the viosterol. This distinction was evident both by biologic assay on rats and by clinical tests of a preventive and curative nature. The outstanding advantage of this method of antirachitic therapy is that it functions automatically as the specific factor is incorporated in the diet of the infant.

Soft-curd Milk: Nature's Food for Infants.—Hill (*Arch. Ped.*, 1931, **48**, 417) states that when soft-curd milk is available, the feeding problem becomes much simpler. Experimental results would indicate that this milk is easily digested without dilution or modification, and that it can be used in a concentrated form. Since there is no dilution, the normal sugar content of the milk is sufficiently high not to require the usual addition of carbohydrate. The use of lactic acid to produce an acid curd apparently is not necessary when soft-curd milk is used It seems possible to supply milk that is sweet and has a normal reaction and has not been abnormally sweetened, nor any other alterations made from its natural state. The use of a natural milk obviously is superior to the use of a milk that is abnormally acid or alkaline in its reaction. There has been an advantage noted in the use of hard-curd milk over soft-curd milk in the manufacture of cheese. This may ultimately free soft-curd milk for use in infant feeding.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

Untoward Results From the Use of Gold Compounds.—Driver and Weller (*Arch. Dermat. and Syph.*, 1931, **23**, 87), in reporting a fatality following the administration of 25 mg. and 50 mg. of gold and

sodium thiosulphate 4 days apart in a woman with lupus erythematosus, take occasion to review the gold compounds in common use and the reactions following their administration, and cite from the literature numerous examples of deaths arising in the course of gold therapy in cutaneous as well as pulmonary tuberculosis. The paper is particularly timely in view of the more widespread knowledge of the value of the salts of gold in lupus erythematosus and their more indiscriminate trial in the tuberculids and closely related dermatoses. The more important reactions from the use of gold may be tabulated as follows:

A. Immediate Reactions. (1) Anaphylactic type—varying degrees of syncope and shock, with nausea, occasional vomiting, flushed face, edema of the lips and face and tachycardia. These symptoms are usually of short duration, but death has resulted. (2) Mild febrile reaction with malaise and headache, usually lasting 4 to 6 hours and rarely for several weeks. (3) Metallic taste in the mouth. (4) A foreign protein reaction, which usually begins about 1 hour after injection, characterized by dull headache, suffusion of the eyes and chill. The symptoms abate within about 0.5 hour.

B. Delayed Toxic Reactions. (1) A syndrome of fever, headache, nausea, occasionally with vomiting, malaise and prostration. Symptoms begin 4 to 6 hours after injection and last from a few days to a week or longer. (2) Stomatitis and gingivitis, usually mild but rarely of an ulcerative and hemorrhagic type. (3) Renal damage—albuminuria and varying degrees of acute nephritis. (4) Hepatitis with icterus. (5) Digestive disturbances ranging from the transient symptoms of the toxic syndrome to ulcerative and hemorrhagic enteritis. (6) Cutaneous eruptions: The picture varies greatly in severity and type, ranging from temporary erythema and urticaria through papular and bullous expression to a dermatitis exfoliativa which resembles that seen from intolerance to the arsphenamins. Itching accompanies all phases of the cutaneous reaction. (7) Hemorrhagic tendency—with hemorrhages into the skin and from the gastrointestinal tract, hemoptysis, epistaxis, hematuria and metrorrhagia.

While mild reactions to gold are quite common, the more severe ones are fortunately rare. Since they occur early in the course of treatment, as a general rule, it is necessary to observe special care at this stage of therapy. An initial dose of 10 mg. is suggested in cases of lupus erythematosus, to be followed at weekly intervals by ascending doses up to 50 mg. In resistant cases the authors suggest a cautious increase of dose to 75 mg. with an upper limit of 100 mg. Numerous authorities attest the equal therapeutic effectiveness of small doses and the incidence of reactions can be greatly lessened by more conservative doses.

Cutaneous Calcinosis.—In reporting a case of calcinosis in a boy, aged 14 years, with multiple calcium tumors on the skin and subcutaneous tissue of the hands, elbows and knees, MALONEY and BLOOM (*Arch. Dermat. and Syph.*, 1931, **23**, 245) review the literature of the subject and classify the forms of calcinosis as follows: *A. Local.* This includes calcification in tumors such as epithelioma, atheroma, dermoid cyst and in pseudoxanthoma elasticum. *B. General.* (1) Metastatic calcinosis—associated hypercalcemia from the destruction of bone through

osteomyelitis, caries or lymphatic leukemia. (2) Metabolic calcinosis —an imperfectly understood disturbance of the calcium metabolism unassociated with destruction of bone. The authors stress the frequent association of calcinosis with scleroderma and sclerodactylia. The clinical picture of cutaneous calcinosis consists of small pea to walnut-sized tumors or plaques occurring on the fingers, hands, wrists, elbows and knees often following the course of the tendons. These tumors frequently perforate through the overlying adherent red skin and give rise to a creamy mass often containing small granules. New lesions are apt to appear in crops. Occasionally calcinosis appears as elevated yellow ridges over the elbows and knees.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Operation for Temporary Sterilization.—In certain cases in which sterilization is indicated it is often desirable that such sterilization be of a temporary nature so that when the indication for the prevention of conception has passed it will be possible to restore the possibility of a future pregnancy. In the usual type of tubal sterilization operation it is quite a difficult matter to restore the continuity of the tube with any degree of assurance as to its future function. The operation which NAUJOKS (*Zentralbl. f. Gynec.*, 1931, **55**, 81) describes as a reversible sterilization operation might be of value in such cases. He points out that the operation should not be attempted when there is pelvic inflammatory disease or any marked destruction of the tubal mucosa as in such cases it would be hardly likely that pregnancy would supervene, but in such cases there is seldom an indication for sterilization in the first place. The essential feature of the operation is that the uterine ends of the tubes are not disturbed so that there will be no difficulty later in attempting to anastomose the tubes to the uterus. The operation consists of a crushing of the outer end of the tube with an enterotriptor of the Roux type followed by a double ligation of the crushed portion with silk ligatures. The crushing should be evenly distributed across the tube and about 10 mm. wide and with sufficient pressure that there is no doubt that both the musculature and mucous membrane of the tube are actually crushed. This portion of the tube then atrophies into a small cord which is impermeable. When it is desired to restore the patulousness of the tube, it is merely necessary to resect the crushed outer portion, preferably with a diathermy knife so that there shall be no bleeding which might tend to seal the new ostium.

Results of Olshausen's Operation.—A review of 3358 cases in which Olshausen's uterine suspension had been performed has been presented by GRAVES and SMITH (*Surg., Gynec. and Obst.*, 1931, **52**, 1028) accompanied by an enthusiastic endorsement of the procedure. Of the cases which were followed for more than 2 years symptomatic cures were obtained in 66.8 per cent, relief was obtained in 27.3 per cent while in 5.6 per cent the operation was a failure. From the standpoint of anatomical results, in 76.9 per cent the uterus was in good position, in 14.2 per cent there was a partial recurrence and in 8.8 per cent there was a complete recurrence. Pregnancy occurred 856 times in 489 patients (17.6 per cent of the traced cases) of which 406 had normal deliveries. Abortions and miscarriages occurred in 197 of the pregnancies while the remainder of the pregnancies terminated in some complicated form of delivery, 132 being instrumental. Of the cases examined after childbirth the uterus remained in normal position in 71.4 per cent, there was a partial recurrence in 12.7 per cent and a complete recurrence in 15.7 per cent. The statement is often made that this operation is frequently followed by intestinal obstruction but in this large and carefully followed series of over 3000 cases there were only 6 known cases of intestinal obstruction. Of these 2 died without operation, while of the 4 that were operated upon 3 survived. The above results seem to be most satisfactory especially when it is remembered that the operation was done in over half of the cases for the cure of prolapse and procidentia. (An authoritative review by one of our foremost gynecologic surgeons. C. C. N.)

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

The Value of the Roentgenologic Examination in Pulmonary Tuberculosis.—Do changes on the film precede those detected by the usual methods of physical examination? SAMPSON and BROWN (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 209) answer that in a surprisingly large number of cases definite changes characteristic of tuberculosis occur in the film long before definite evidence of abnormal physical signs can be detected. How early in the course of the disease can definite changes be detected? This question the writers do not answer specifically. They point out, however, that in school children they believe roentgenologic evidence of pulmonary tuberculosis exists in many cases for years before symptoms arise that focus attention on the lungs. The incidence of the five cardinal diagnostic data in 1367 cases diagnosed

pulmonary tuberculosis from 1478 consecutive cases in the Trudeau Sanatorium were as follows: Tubercle bacilli, 61.5 per cent; râles, 68.5 per cent; Roentgen ray, +99 per cent; hemoptysis, 33.5 per cent; pleurisy, 12 per cent. The roentgenogram can usually be relied upon to register the extent of the lesion, frequently revealing more disease than is detectable otherwise, and in many instances bringing to light foci which would otherwise be overlooked.

Palliative Therapy of Malignant Growths.—That 80 per cent of all persons suffering from cancer are incurable by surgery is the estimate of Wood (*Radiology*, 1931, **16**, 291). A few of these patients may be cured, and more can have their lives prolonged over a considerable period of years by radiation. Another group can gain relief from pain and a certain amount of psychic comfort from irradiation, though there be no evidence that life is prolonged. Too much stress has hitherto been laid on the attempt at permanent cure by heavy radiation, which too often renders the patient's life miserable or actually shortens it.

Roentgenologic Changes in Sarcoid and Related Lesions.—Boeck's sarcoid, which is characterized by the formation of nodules in the cutaneous and subcutaneous tissues, sometimes associated with fibrocystic changes in the bones or a fibrous infiltration in the lungs, is generally regarded as a form of infection with the bacillus of tuberculosis, although other hypotheses as to its origin have been advanced. Kirklin and Morton (*Radiology*, 1931, **16**, 328) have reviewed the roentgenologic observations in 6 cases, of which 2 had demonstrable changes in the bones, 2 in the lungs and 2 in both the bones and the lungs. In the lungs the typical abnormality is a bilateral, fairly dense, diffuse, linear infiltration of the midportion or bases, superimposed on which are discrete opaque areas, ranging in size from miliary nodules to nodules 1 cm. in diameter. The apexes are not affected, and there are no signs of pleurisy or fluid. Of the bones, the phalanges of the hand or foot are most often attacked. The disease of the bone seems to be first evident as a thickening of the trabeculæ in the end of the phalanx. Punched-out areas appear and later there is a peculiar combination of destruction and repair. The whole phalanx may be affected. If the process is arrested and healing occurs the bone may return almost to normal, but usually considerable mutilation results.

Bone Metastasis.—Three hundred and thirty-four cases of malignant metastasis in bone were studied by Copeland (*Radiology*, 1931, **16**, 198). Of these, 100 cases were consequent on cancer of the breast. The bones most frequently involved in order of incidence were the spine, pelvis, femur, skull, ribs and humerus; metastasis in the forearm and leg was infrequent. The lesions were most often multiple and were single in only one-fourth of the cases. Metastasis occurred in 22 cases of hypernephroma; bones affected, in order of frequency, were the humerus, spine, femur, pelvis, ribs, bones of the feet, skull and sternum. Cancer of the prostate produced metastasis in 134 cases and most frequently involved the pelvis and vertebræ, rarely the femurs, lower end of the tibia and the skull. Malignant disease of the testicle was the primary source in 2 cases, of the bladder in 1, of the ovary in 2 and of the thyroid

in 6. Seven patients with cancer of the stomach had metastasis to the bones, the order being ribs, pelvis and femur, vertebræ, sternum, skull and scapula. Metastasis to bone was found in 4 cases of cancer of the lung; a wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull.

Intravenous Urography.—Braasch (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 196) believes that uroselectan will be only a forerunner to mediums of greater excellence, such as skiodan, which is about to be placed on the market. The author's limited experience with the latter leads him to believe that most of the claims advanced for it are substantiated. Among its advantages are earlier excretion, absence of subjective reaction to its administration and increased clarity of the urograms. It makes available a method which sometimes permits of diagnosis without the necessity of obtaining cystoscopic data. Its universal use will be limited because knowledge of urographic interpretation is necessary and because cystoscopic and other clinical data are usually necessary before exact diagnosis can be made. The greatest value of intravenous urography to the urologist will be its employment in cases in which cystoscopy and ureteral catheterization are contraindicated or impossible. It will be particularly valuable in children. With the present medium the films are still frequently too inexact for interpretation. The greatest weakness of the method lies in its failure to accurately outline minor deformities. Its value will be greatest in the presence of urinary stasis. Failure of renal visualization does not necessarily indicate that renal function has been destroyed. It is frequently of value as a visual functional test and often will suffice to determine the presence of a good kidney on the opposite side from that to which symptoms are referred. Mediums which contain organically combined iodin offer ideal solutions for use in retrograde pyelography.

The Effect of Roentgen Rays on the Heart.—Following up their previous work which tended to show that repeated exposures of the hearts of rats to the Roentgen rays produced definite cardiac lesions, Warthin and Pohle (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 625) have endeavored to establish the toleration dose over the precordium of rats. This they found to be 500 r. In cases in which this dose was attained or exceeded no clinical symptoms were observed which might indicate cardiac injury. The only gross pathologic change consisted of a dilatation of the right ventricle. Microscopically, there was Zenker's necrosis in varying degrees, pycnosis of nuclei, and increase in stroma nuclei, with small foci of lymphocytes.

Five Years' Experience With Oral Cholecystography.—After 5 years of daily experience with oral cholecystography, and the use of every known method of administering the dye, Stewart and Illick (*Am. J. Roent. and Rad. Therap.*, 1931, **25**, 602) still believe that the oral method is the most satisfactory and reliable. If there are any advantages in the intravenous, its very real dangers counterbalance them, and it is not, in the opinion of the writers, a safe office procedure. The oral method is universally applicable and has proved to be entirely reliable. Any dissatisfaction with the Graham test, the writers believe, is due to improper technique.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Disseminated Encephalomyelitis.—GRINKER and BASSOE (*Arch. Neurol. and Psychiat.*, 1931, **25**, 723) present, in detail, 4 cases of encephalomyelitis from a clinical and pathologic point of view. They compare these examples with examples of other forms of encephalitis which they have studied, and propose a broad pathologic classification outlining the etiologic conclusions which they feel are justifiable. In Case 1 there was a history of a slight upper respiratory tract infection; five days later there occurred bulbar and cord symptoms, with low-grade fever; death occurred from medullary involvement in nine days. Autopsy revealed multiple perivascular softenings throughout the neuroaxis. In commenting on this case they remark that the entire picture was identical with that which has been described in encephalomyelitis following the use of cowpox vaccine and rabies vaccine, and in encephalitis measles and variola; that "The perivascular, inflammatory, complete and incomplete softenings, with moderate lymphocytic reaction, are typical of these forms of infections;" and ask, "Are all these cases, then, examples of identical virus infections only precipitated by exanthematous disease, vaccinations and nonspecific infections . . . ?" Case 2 was a child in which leg paresis and hemiplegia developed gradually; the opposite leg became involved; stupor developed; a terminal fever led to death in 23 days after the onset. Necropsy revealed a disseminated encephalitis. The extraordinary dissociation of the inflammatory reactions and the patches of demyelinization were the high points of interest in this case. The diffuseness of the infiltrations, the character of the cells and their presence distant from the lesions with multiple sclerosis and Schilder's disease would suggest them to be of toxic degenerative origin. Case 3 had severe medullary symptoms, with low-grade fever; there were several remissions over a period of 5 months, then progression with cord symptoms and death. Autopsy showed a subacute disseminated encephalomyelitis. Here the clinical observations indicated clearly that the sites of the lesions were in the brain stem. The nature of the pathologic process was surmised from the suddenness of the onset, the febrile reaction and the relatively rapid course. Case 4 had a previous acute infectious episode, with medullary symptoms. The patient recovered with severe residua; a relapse followed with febrile reaction. In commenting on this case the authors remark that it seems probable that the patient had had an acute disseminated encephalomyelitis, with severe damage to the medulla. The paper continues with a rather vivid discussion of the etiologic factors and the pathologic findings of

the encephalitides in which the authors state that: "The etiologic status of the diffuse encephalitides, including Schilder's disease, has not been solved after many years of pathologic study. No adequate criteria for not considering them infections in origin and searching for their bacterial cause have been advanced by neuropathologists." "The pathologic observations have been typical for all cases. Multiple perivascular lesions are found, particularly about the venules, consisting of complete or incomplete softenings or, in the milder cases or younger areas, demyelinization with relatively less axonal destruction. The lesions seem to have a predilection for white matter of both the spinal cord and the cerebrum. A relatively moderate mesodermal reaction in the form of perivascular lymphocytic infiltration has been noted." Still further along they remark: "Thus, it seems that a variety of clinical conditions, including vaccination against smallpox or rabies and exanthematous diseases, such as measles and smallpox in human beings, produce an identical pathologic condition. . . . If a pathologic classification of the central nervous infections were to be proposed on the basis of distinct, regularly occurring microscopic changes, it is apparent that each group would embrace examples of more than one clinical syndrome. Exclusive of syphilis, the parasitic infections and the changes in the brain in sepsis, with its miliary abscesses, such a classification of nonsuppurative encephalitide would be as follows: (1) Severe focal demyelinization, less severe axonal damage, microgliosis, mild or absent perivascular lymphocytic infiltration, gliosis (chronic multiple sclerosis and certain cases of acute multiple sclerosis). (2) Focal lesions of incomplete or complete softenings, not perivascular, microgliosis, varying degree of lymphocytic infiltration, vascular proliferation and connective-tissue scar formation (acute disseminated encephalomyelitis and certain cases of acute multiple sclerosis). (3) Focal perivascular incomplete softenings, involving the whole nerve fiber, coalescing of lesions to form softenings, microgliosis, mild lymphocytic reaction, secondary gliosis (cowpox and rabies vaccine, measles, varicella and variola and certain cases of disseminated encephalomyelitis). (4) Diffuse subcortical destruction of nerve fibers, probably beginning in the myelin sheaths, mild or absent lymphocytic infiltration, primary progressive gliosis with secondary regressive glial forms, connective-tissue scar (Schilder's disease and disseminated encephalitis). (5) Diffuse but relatively selective (basal nuclei, medulla or anterior-horn cells) ganglion-cell destruction, abundant perivascular and tissue lymphocytic infiltration, mild microgliosis, white matter spared (rabies, epidemic encephalitis and Heine-Medin's disease). (6) Hyperplastic meningeal reaction, regressive changes in capillary endothelium, formation of new bloodvessels, degenerative changes of ganglion cells, absent mesodermal infiltrations (toxic encephalitis secondary to acute infections and exogenous toxins such as lead).

Encephalographic Studies in General Paresis.—Ebaugh, Dixon, Kiene and Allen (*Am. J. Psychiat.*, 1931, **10**, 737) report their study of 97 encephalographic studies made upon 70 cases of general paresis. These cases of general paresis they have divided into three groups: (*a*) Cases that show definite and characteristic findings of mental deterioration—in these cases advanced parenchymatous findings have

occurred; (*b*) organic reactions with psychoses of functional coloring—this group includes cases of general paresis in which therapy may possibly arrest the pathologic process and restore the patient for either transient or permanent periods—the psychosis simulates the functional disturbances seen in the manic excitements and the depressions as well as other functional reaction types; (*c*) transitory psychoses without signs of deterioration—this group includes delirious reactions and neurologic irritative phenomena on the basis of exacerbated meningovascular and endarteritic disease. The encephalographic studies of the Group A paretics indicated, on the whole, an obliteration of the cortical cerebrospinal fluid pathways, especially in the frontal and parietal areas with dilatation of the basal cisternæ. The authors assume that there has been, apparently, a damming up of the cerebrospinal fluid over the cortex of these areas. (This obliteration of the cortical spinal fluid pathway is known as "arachnoiditis.") In other cases of this group they found atrophic areas that seemed to be combined with "arachnoiditis." In still other instances they noted that there was an apparent reduplication of the cortical fluid pathways. In several of these cases marked insular atrophy was found. In the study of the encephalograms of Group B paretics similar findings to these described in Group A were noted. In general, however, they found that the areas of cortical atrophy appeared to be less marked. The "arachnoiditis," too, was found to be less pronounced. The encephalograms of the paretics grouped under C showed many cortical markings, slight cortical atrophy and very patchy arachnoiditis. In addition to these studies the authors present a comparison of encephalograms before and after nonspecific therapy of general paresis. Here they remark: "The most striking encephalographic pattern shown after malaria therapy consisted in the clearing up of 'arachnoiditis' manifest before malaria treatment in 3 cases. The malaria treatment apparently has released the obstructing factor in the cerebrospinal fluid pathways, so that full drainage with wider areas of fluid release has occurred over the cortex." As a result of this, they find that there is a decrease in the dilatation of the basal cisternæ and further atrophy of the brain is brought into view. They discuss rather adequately the technique of encephalography and the complications encountered, finally concluding that: (1) Encephalography in careful hands is a safe clinical procedure; (2) the encephalographic finding appears to be definitely related to the pathology present in the stage of general paresis studied; (3) clinical improvement and arrest in many of the cases studied appears to be closely correlated with the encephalographic findings present; (4) after sufficient data are collected this method may prove to be of great benefit in further clinical and prognostic groupings of this disease.

Some Principles in the Treatment of Behavior Problems in Children.—Lawson G. Lowrey (*Arch. Neurol. and Psychiat.*, 931, **25**, 884) presents rather briefly the essential points in the treatment of behavior problems of children. He divides the treatment into two parts: (*a*) direct, and (*b*) indirect. The direct measures comprise those in which the physician and his assistants deal directly with the patient. The indirect method is defined as the "social-manipulative," intended to convert the environment of the child into a source of positive rather

than of negative stimuli. In his discussion of the manipulation of the environment he remarks that the measures used may be divided into two major groups: (1) manipulation of things—the adjustment of the environment so that the reaction of the personality to it will be more harmonious, and (2) the manipulation of people—in order that the minimum friction exists between the contacting personalities. In discussing the patient he states that the child is a complicated personality at whatever his stage of development he may be in, that for the creation of an organized personality several points are needed, *viz.:* (*a*) a satisfaction of a feeling of achievement by the child; (*b*) recognition by people that he is an individual; (*c*) affectional relationships with other persons; (*d*) a feeling of belonging to a group. The author remarks that he and his colleagues have worked out a "new, simple five-fold classification of the common groups of factors involved in the causes of behavior disorders, which is important in focusing treatment." Group I, the gross mental deviations—psychoses, feeble-mindedness, and epilepsy, and postencephalitic behavior disorders. Group II, gross physical deviations. Group III, the neuroses. Group IV, the complexes and conflicts below the neurotic level. Group V problems, the result of faulty training or ignorance. These groups are discussed adequately, and the paper is concluded with a general outline for a program of treatment of the problems dependent upon the age of the child.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Selective Distribution of Diphtheria.—The explanation for the selective infection of certain individuals with Bacillus diphtheriæ is still far from complete, despite the fact that there have been available to the investigator probably more material facts than for any other infectious disease. Bacteriologic diagnostic methods have improved and have been used extensively for a long time. Toxicity of strains is relatively easy to determine. Antitoxin has been a potent help. The Schick test has added very much to our knowledge and yet there remain many factors about which little is known. It is therefore of great interest and value to have DOULL (*J. Prev. Med.*, 1930, **4**, 371) review the present situation of the problems which remain unsettled. He gives as postulates: (1) A case of diphtheria signifies infection overcoming host resistance. (2) Carrier infection with a toxin-producing organism signifies effectual host-resistance. (3) A negative reaction to the Schick test in those untreated and with no history of diphtheria implies

one or more prior subclinical infections. The importance of exposure or dosage is fully discussed as well as that of determined host-resistance in its bearing on age and sex incidence, the infrequency of diphtheria in the negro and in the tropics, and the effect of anatomic factors such as removal of the tonsils. Nevertheless there remain many examples of peculiar local, seasonal and cyclical variations in which the determining factors are obscure, and he suggests that these may be due to the incidence of more pathogenic strains of the bacillus. It is of particular interest that the great pandemic of diphtheria, beginning just after the middle of last century as local epidemics, assumed great malignancy which lasted for twenty or thirty years, after which a decline began, with occasional fluctuations, which has continued to the present.

Studies on Inflammation.—In a series of experiments upon inflammation, MENKIN (*J. Exp. Med.*, 1931, **53**, 171) has shown that solutions of ferric chlorid, trypan blue and horse serum, are more or less fixed at a site of inflammation in rabbits when injected intravenously or directly into the inflamed area. Trypan blue solution injected subcutaneously at the periphery of a superficial area of inflammation did not diffuse into the site of inflammation. The author has demonstrated coagulation or precipitation of horse serum and ferric chlorid by inflammatory exudates, while normal blood serum did not produce this result. Trypan blue was not affected by such exudates nor by normal blood serum. Histologic study, however, indicated that coagulation or precipitation was a secondary factor in the fixation of foreign substances, the primary agent being mechanical obstruction caused by a network of fibrin about the site of inflammation and by thrombosis of lymphatics. In further studies the author (*J. Exp. Med.*, 1931, **53**, 179) showed that in frogs, trypan blue injected into the circulating blood or directly into an area of inflammation was fixed at the inflammatory site. If the dye was injected at the periphery of an inflamed area it failed to enter the site of inflammation. Histologic study again indicated that the failure of diffusion of dye out of or into the inflamed area was the result of occlusion of lymphatic vessels and the presence of a network of fibrin in the inflamed area.

Compensatory Hypertrophy of the Adrenal Cortex in the Rabbit.—In carefully controlled experiments MACKAY and POLLAND (*J. Pathol. and Bacteriol.*, 1931, **34**, 73) found that the removal of one adrenal in the rabbit was followed by compensatory hypertrophy of the remaining gland. The hypertrophy was found to be entirely in the cortex. The increase in size evidently took place within the first month since hypertrophy was just as great at the end of 30 days (41 per cent) as at the end of 150 days (37.7 per cent). Compensatory hypertrophy of the adrenal cortex in the rabbit was less in degree than that which followed the removal of one adrenal in the rat.

Observations on Melanosis Coli.—STEWART and HICKMAN (*J. Pathol. and Bacteriol.*, 1931, **34**, 61) have made a study of melanosis coli in two series of cases; the first consisted of 600 unselected autopsies at all ages and the second of a consecutive series of 100 cases of carcinoma of the

colon. The pigment was found to be limited in most cases to the large intestine and appendix, and ranged in intensity from gray or buff through dark gray or brown to inky black. The melanin-like pigment was found within larger mononuclear cells in the mucous membrane of the gut. The severe degrees of pigmentation were comparatively rare, but including the slighter forms, the incidence in the unselected series was 11.2 per cent. In persons over the age of 40 years the incidence was higher (17.7 per cent) and in cases of carcinoma of the colon reached about 50 per cent. In most of the latter instances the melanosis was more intense above than below the growth. The authors concluded that the chief causative factor of melanosis coli is chronic intestinal stasis, whether resulting from organic obstruction or from simple constipation. They subscribed to Pick's theory of the mode of formation of the pigment, namely, that aromatic protein disintegration products are absorbed from the colon and converted into melanin within the connective-tissue cells by the action of a tyrosinase-like ferment.

Experimental Liver Necrosis from Shale Oil.—Polson (*J. Pathol. and Bacteriol.*, 1931, **34**, 5) was successful in producing liver necrosis in rabbits and rats by the intraperitoneal administration of shale oil. It required ten to fifteen times the dose given to rabbits, weight for weight, to produce lesions in rats. Heating the oil to a temperature of 200° C. previous to its administration did not diminish its effect. The non-carcinogenic residue, however, produced only slight changes in liver. The less severe necroses were confined to the central portion of the liver lobule, while in the more severe, the liver cells were completely wiped out with exception of a few swollen and vesicular cells about the periphery of the lobule. In these cases only the delicate fibrous framework of the lobule and remnants of the cells remained except at the periphery. In the cases of acute necrosis no cellular reaction was observed, but in the subacute type the areas of necrosis were bordered by zones of lymphocytes and polymorphonuclear leukocytes. Hemorrhages were present in the necrotic tissue and the surviving cells about the periphery were loaded with neutral fat. In the longer experiments the portal tracts were enlarged by fibrosis. The lesions formed by graduated doses ranged from acute necrosis to cirrhosis of liver and were almost indistinguishable from the "atrophic" series in man. The experimental difficulties arising from the presence of spontaneous disease were overcome by laparotomy and biopsy of the liver.

Asbestosis Bodies in the Sputum: A Study of Specimens from 50 Workers in an Asbestos Mill.—Examination of the sputum from 50 workers in an asbestos mill by Simson and Strachan (*J. Pathol. and Bacteriol.*, 1931, **34**, 1) showed the presence of asbestosis bodies in 48 of the cases. The age of the workers varied from 17 to 50 years, and the length of exposure to asbestos from 7 months to 9 years, the great majority having worked with asbestos for more than 3 years. Cough was present in every case, dyspnea in all but 10 and loss of weight in all but 21. Examination of the sputum for tubercle bacilli was negative in every case. Nearly all the specimens contained thin watery mucoid material, though it was occasionally thick while pus cells were present in all specimens, though only a few contained obvious pus. The

sputa were examined by direct smear and also by the antiformin method. The former was preferred because it showed the cytology of the specimen and the intracellular development of the asbestosis bodies. The bodies were always contained within "dust cells" and varied greatly in size and shape. Some were long and thin and projected beyond the normal outline of the cell, being covered by cytoplasmic prolongations. The asbestos fibers were thinly coated with a greenish or golden-yellow material which constantly gave the Prussian blue reaction. It was suggested by the authors that the asbestosis bodies were formed by the deposition on the asbestos fibers of an iron-containing substance elaborated by the cell.

Aneurysms of the Abdominal Aorta.—Ricci (*Archivio di Patologia e Clinica Medica*, 1930, **10**, 78) reviews the symptomatology of aneurysms in the abdominal aorta, their pathogenesis, diagnosis and therapy. Pain appears always of exceptional importance in the symptomatology, because of its early appearance and its peculiar characteristic. The study of the clinical features and the pathologic anatomy of a very interesting case of an aneurysm in the abdominal aorta, in which there existed, despite the large volume of the aneurysm, a perfect synchronism between the humeral pulse and that of the femoral artery, demonstrates how the retardation of the femoral pulse may be quite lacking when the contents of the aneurysmal sac are well organized.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Studies on Tuberculosis. The Relation of the Tubercle and the Monocyte-lymphocyte Ratio to Resistance and Susceptibility in Tuberculosis.—Doan and Sabin (*J. Exp. Med., Suppl. No. 3*, 1930, **52**, 113) state that in rabbits receiving a standard dose of bovine tubercle bacilli a high preinfection monocyte-lymphocyte ratio in the circulating blood has been correlated with the development of an acute fulminating tuberculous infection; but with an average or low index the course of the disease has varied. Susceptibility has been further marked by the promptness with which the M/L index rose after infection and with its maintenance at a high level; resistance, on the other hand, has been evidenced by a continued low index. The M/L index is one measure of resistance to tuberculosis. Some evidence has been presented to show that when monocytes, the forerunners of the epithelioid cell, are decreased through the action of an antiserum a greater proportion of

the animals survive into the chronic stage of the disease than of the controls. The production of tubercular tissue in considerable quantity by injection into the tissues of the phosphatid or liquid saturated fatty acid from the tubercle bacillus does not render the animal allergic, and seems definitely to lower resistance to the disease upon subsequent infection with tuberculosis. The degree to which the tissues react specifically with the formation of new epithelioid cells is indicated by the amount of the change in the M/L index in the blood. The differences observed in individual animals in the amount of tissue reaction to a given amount of phosphatid derived from the tubercle bacillus are definite and are similar to those long noted in connection with humoral antigen-antibody responses with proteins. Both in tuberculosis itself and after intraperitoneal injections of the phosphatid the relation of monocyte to lymphocyte in the blood before death has been a measure of the extent of the epithelioid and lymphoid proliferation found at autopsy. Hence, the M/L ratio can be taken as an index of the relative abundance of these cells in the tissues. Antigenic intravenous doses of the phosphatid itself, or of antiphosphatid serum, given either before or after infection, may give a slight protection to an animal if the dose of infecting organisms be not too great. Taken together, the observations of the present paper implicate the monocyte and its derivative, the epithelioid cell, when harboring living bacilli, as factors in the spread of tuberculosis in the animal. The type of reaction of an animal to the lipoids of the tubercle bacillus, whether predominantly cellular or humoral, may be a decisive factor in determining resistance on the one hand and susceptibility on the other.

A Study of Ventilation and Respiratory Illness in New York Schools; Comparison of Window-gravity Ventilation and of Unit Fan Ventilation with Varying Air Flow.—The original work of the New York Commission on Ventilation called attention to the possibilities of ventilating schoolrooms with a relatively low flow of cool air by the use of window inlets and gravity exhaust ducts. These early studies and those of Greenburg, at New Haven, Childs, at Cleveland, and Butch and Reavis, all suggested that schoolrooms ventilated by the window-gravity method were not only as satisfactory as those ventilated by plenum fans but were actually superior to them—the window-gravity rooms in all four studies showing less respiratory disease among the pupils than did rooms ventilated by fans delivering 30 cubic feet of air per pupil per minute. More recent studies of the New York Commission have, however, brought out very clearly certain possible errors in the use of respiratory disease data as a measure of the healthfulness of the schoolroom. They indicate that not only age and sex but also social and economic status of pupils (as measured by nationality of parents) markedly affect respiratory disease absenteeism; and that respiratory disease in attendance is so affected by subjective judgment that it cannot fairly be used as a criterion if the observations of different observers are compared. On the other hand, results of studies made at Syracuse appear to demonstrate that when age, sex and nationality stock are duly balanced high consistent and significant results may be obtained and that even records of respiratory disease in attendance are concordant when the results are obtained by the same observer. The

present study (*Am. J. Hyg.*, 1931, **13**, 235) was designed to check the results in Syracuse in a different city and using unit ventilation instead of a central plenum system for the comparison of air flow and also to compare unit fan ventilation with the window-gravity system (which was not represented in Syracuse). As in the Syracuse studies, it appears that when school populations are balanced as to age, sex and nationality stock, and when the personal equation of the observer is held balanced, concordant and consistent results may be obtained from a study of school absenteeism and of respiratory illness among pupils in attendance. A study of the health of pupils in schoolrooms ventilated by unit ventilators shows that reducing the rate of air flow from the standard figure of 30 cubic feet per pupil per minute to approximately one-half that amount was not attended by any harmful effects so far as could be observed. The teachers preferred the rooms with low air flow on account of freedom from drafts and the lessened noise of the unit motors. A comparison of schoolrooms ventilated with unit ventilators and of those ventilated by window inlets with gravity exhaust shows that the simpler gravity process is quite as satisfactory from the health standpoint as is the system involving the use of fans.

Ultraviolet Radiation and Resistance to Infection: Intranasal Infection With the Pneumococcus and With Bacterium Lepisepticum in the Rabbit.—Hardy and Chapman (*Am. J. Hyg.*, 1931, **13**, 255) performed a series of experiments to test the effect of ultraviolet radiation on the resistance of rabbits to pneumococcus Type I and Bacterium lepisepticum infections. It is possible that the rabbit is a poor animal for experiments of this type, as its rapid rise in temperature in direct sunlight makes it probable that the animal never receives any considerable amount of ultraviolet radiation under normal circumstances. The radiation was given several times a week over a period of many weeks before inoculation, and the dose was varied from a suberythemal level to a heavy dose causing a severe burn. The average results of five experiments with artificial ultraviolet radiation from a mercury arc and intranasal inoculation with the pneumococcus showed no difference in attack rate or mortality rate between the irradiated group and the controls. Blood count determinations showed no definite difference in the leukocytic reactions of the irradiated and control groups among animals escaping infection. The irradiated animals contracting the disease showed a slightly higher and more rapid leukocytosis than did the infected controls, with a less marked decrease in lymphocytes. The average of three experiments with exposure to direct sun or north sky light through vitaglass showed that both the percentage of infection and the mortality rate after inoculation with pneumococcus Type I was higher in the irradiated animals than that in a control group kept inside. Similar experiments performed with mercury arc radiation and infection with Bacterium lepisepticum showed that radiation had no effect on the susceptibility to infection, although the mortality rate was somewhat lower in the irradiated group. A variation in the amount of ultraviolet, from a marginal erythema to a heavy but subulcerating dose, had no correlation with resistance to the respiratory infections used. The effect of radiation on antibody formation was also investigated. In the pneumococcus infec-

tion experiments the average complement-fixation titer for the irradiated rabbits was slightly higher than for the controls; but in the Bacterium lepisepticum experiments the average titer for the two groups was precisely the same. There was no relation between the titer and the amount of radiation given. In rabbits immunized with killed pneumococci radiation did not accelerate the production of antibodies or increase the amount above the normal.

Water-borne Typhoid Fever Still a Menace.—WOLMAN and GORMAN (*Am. J. Pub. Health*, 1931, **21**, 115) state that while the typhoid fever death rate in the United States and Canada has made a phenomenal drop since 1900, many large water-borne typhoid outbreaks have occurred during the last decade. Special attention is needed for better control over the safety of water supplies in small cities, as 64.9 per cent of the outbreaks in the United States and 77.5 per cent of those in Canada occurred in those of 5000 population and under. A study of the causes of 282 outbreaks shows clearly the need for more attention on the part of water works and health officials to supervision and control over treatment processes, especially over disinfection where pollutional loads on treatment plants are high or where chlorination is the only safeguard. Over three-quarters of the water-borne illness reported in the United States during the decade 1920–1929, representing 40 per cent of the outbreaks, was due primarily not to pollution of the raw water at its source, but to defects in the system for collecting, treating, storing or distributing of the water for public consumption. Unprotected cross-connections between polluted fire supplies and public water systems were the most important single cause contributing to water-borne outbreaks during the decade 1920–1929 and demand the most active attention of health and water-works officials. During the decade there were 5 repeat water-borne outbreaks in one city from the same cause, and repeat outbreaks in four from different causes. The courts in both the United States and Canada are increasingly holding cities and water companies liable for heavy financial damages for illness resulting from pollution of public supplies.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.